Evidence Report/Technology Assessment
Number 193

Preventing Alzheimer's Disease and Cognitive Decline

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA 290-2007-10066-I

Prepared by:
Duke Evidence-based Practice Center
Durham, North Carolina

Authors:
John W. Williams, M.D., M.P.H.
Brenda L. Plassman, Ph.D.
James Burke, M.D, Ph.D.
Tracey Holsinger, M.D.
Sophiya Benjamin, M.D.

AHRQ Publication No. 10-E005
April 2010

This report is based on research conducted by the Duke Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2007-10066-I). The findings and conclusions in this document are those of the author(s), who are responsible for its contents, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

Suggested Citation:
Williams JW, Plassman BL, Burke J, Holsinger T, Benjamin S. Preventing Alzheimer's Disease and Cognitive Decline. Evidence Report/Technology Assessment No. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.

No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in this report.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) requested and provided funding for this report. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Jennifer Crossman, M.D.
Acting Director
National Institutes of Health (NIH)
Office of Medical Applications of Research (OMAR)

Beth A. Collins Sharp, Ph.D., R.N.
Director, EPC Program
Agency for Healthcare Research and Quality

Steven Fox, M.D, S.M., M.P.H
EPC Program Task Order Officer
Agency for Healthcare Research and Quality

Acknowledgments

The authors thank the following individuals: for help with literature search and retrieval, Connie Schardt; for statistical support, Victor Hasselblad, Ph.D.; for assistance in the preparation of evidence tables, Remy Coeytaux, M.D., Ph.D.; Jennifer McDuffie, Ph.D.; Ravi Dhurjati, D.Phil.; Carolina Aponte Urdaneta, M.D.; and Katie Dore, P.A-C.; for project management, Julian Irvine, M.C.M.; for editorial assistance, Rebecca Gray, D.Phil.; and for research assistance, Alice Thacher and Vincent Miller.

Structured Abstract

Objectives: To assess whether previous research on purported risk or protective factors for Alzheimer's disease (AD) and cognitive decline is of sufficient strength to warrant specific recommendations for behavioral, lifestyle, or pharmaceutical interventions/modifications targeted to these endpoints.

Data Sources: MEDLINE® and the Cochrane Database of Systematic Reviews. Additional studies were identified from reference lists and technical experts.

Review Methods: A group of experts in the field developed the list of factors to be evaluated in preparation for an upcoming National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) State-of-the-Science Conference addressing the prevention of AD and cognitive decline. We grouped the factors into the following categories: nutritional factors, medical conditions and prescription and non-prescription medications, social/economic/behavioral factors, toxic environmental factors, and genetics. Outcomes of interest were the development of AD or cognitive decline. Both observational and intervention studies were evaluated. Studies were evaluated for eligibility and quality, and data were abstracted on study design, demographics, intervention or predictor factor, and cognitive outcomes.

Results: A total of 25 systematic reviews and 250 primary research studies were included**.** Only a few factors showed a consistent association with AD or cognitive decline across multiple studies, including both observational studies and randomized controlled trials (when available). Such factors associated with increased risk of AD and cognitive decline were: diabetes, epsilon 4 allele of the apolipoprotein E gene (APOE e4), smoking, and depression. Factors showing a fairly consistent association with decreased risk of AD and cognitive decline were: cognitive engagement and physical activities. A consistent association does not imply that findings were robust, as the data were often limited, and the quality of evidence was typically low. In addition, the modification of risk for reported associations was typically small to moderate for AD, and small for cognitive decline. Some of the factors that did not show an association with AD or cognitive decline in this review may still play an influential role in late-life cognition, but there was not sufficient evidence to draw this conclusion. Many of the factors evaluated are not amenable to randomization, so rigorous observational studies are required to assess their effect on AD and cognitive decline.

Conclusions: The current research on the list of putative risk or protective factors is largely inadequate to confidently assess their association with AD or cognitive decline. Further research that addresses the limitations of existing studies is needed prior to be able to make recommendations on interventions.

Contents

Executive Summary 1

Evidence Report 11

Chapter 1. Introduction 13
- Scope of the Problem 13
- Risk Factors for Alzheimer's Disease and Cognitive Decline 14
- Purpose of this Evidence Report 15
- Role of the Technical Expert Panel 15
- Organization of this Report 16

Chapter 2. Methods 17
- Introduction 17
- Key Questions 17
- Analytic Framework 19
- Literature Review Methods 19
- Peer Review Process 23

Chapter 3. Results 25
- Literature Search Results 25
- Measurement of Cognitive Outcomes 29
- Key Question 1 – Factors Associated with Reduction of Risk of Alzheimer's Disease 30
- Key Question 2 – Factors Associated with Reduction of Risk of Cognitive Decline 141
- Key Question 3 – Interventions to Delay the Onset of Alzheimer's Disease 261
- Key Question 4 – Interventions to Improve or Maintain Cognitive Ability or Function 267
- Key Question 5 – Relationships Between Factors Affecting Alzheimer's Disease and Cognitive Decline 284
- Key Question 6 – Future Research Needs 295

Chapter 4. Discussion 303

Chapter 5. Conclusions 307

References Cited in the Evidence Report 311

Acronyms and Abbreviations 325

Figures

Figure 1. Analytic framework 19
Figure 2. Literature flow diagram 26
Figure 3. Meta-analysis of three cohort studies on homocysteine and risk of developing AD 75
Figure 4. Meta-analysis of six cohort studies on statins and risk of developing AD. 88
Figure 5. Funnel plot of standard error by log hazard ratio for statins and risk of developing AD 89
Figure 6. Meta-analysis of eight cohort studies on NSAIDs and risk of developing AD 98
Figure 7. Meta-analysis of nine cohort studies on physical activity and risk of developing AD 119

Tables

Table 1. Exposures/interventions evaluated in this report 18
Table 2. Inclusion and exclusion criteria 20
Table 3. Included systematic reviews 27
Table 4. B vitamins and folate and risk of developing AD 32
Table 5. Antioxidant and multivitamin use and risk of developing AD 37
Table 6. Omega-3 fatty acids and risk of developing AD – study characteristics and results from studies reviewed by Fotuhi et al., 2009 44
Table 7. Omega-3 fatty acids and risk of developing AD – recent cohort studies 47
Table 8. Intake of various types of fat and risk of developing AD 49
Table 9. Mediterranean diet and risk of developing AD 51
Table 10. Intake of fruit and vegetables and risk of developing AD 54
Table 11. Total intake of calories, carbohydrates, fats, and protein and risk of developing AD 56
Table 12. Diabetes mellitus and risk of developing AD 60
Table 13. Metabolic syndrome and risk of developing AD 64
Table 14. Hypertension and risk of developing AD 67
Table 15. Homocysteine and risk of developing AD 73
Table 16. Obesity and risk of developing AD 77
Table 17. Traumatic brain injury and risk of developing AD – results from case-control studies reviewed by Fleminger et al., 2003 78
Table 18. Traumatic brain injury and risk of developing AD – cohort studies 81
Table 19. Depression and risk of AD – results from stratified analyses by Ownby et al., 2006 82
Table 20. Depression and risk of developing AD – recent cohort studies 84
Table 21. Statins and risk of developing AD 86
Table 22. Antihypertensives and risk of developing AD 91
Table 23. NSAIDs and risk of developing AD 96
Table 24. Gonadal steroids and risk of developing AD – results from stratified analyses by LeBlanc et al., 2001 99
Table 25. Childhood socioeconomic status and risk of developing AD 101

Table 26. Education and risk of developing AD – results from studies reviewed by Caamano-Isorna et al., 2006 103
Table 27. Years of education and risk of developing AD....105
Table 28. Occupation and risk of developing AD 107
Table 29. Social engagement and risk of developing AD 111
Table 30. Cognitive activities and risk of developing AD....116
Table 31. Physical activity and risk of developing AD 121
Table 32. Leisure activities and risk of developing AD 130
Table 33. Smoking and risk of developing AD – results from studies reviewed by Anstey et al., 2007 133
Table 34. Tobacco use and risk of developing AD – recent cohort studies....134
Table 35. Alcohol use and risk of developing AD – results from studies reviewed by Anstey et al., 2009 136
Table 36. Toxic environmental factors and risk of developing AD – characteristics of studies reviewed by Santibanez et al., 2007 137
Table 37. B vitamins and folate and risk of cognitive decline....143
Table 38. Other vitamins and risk of cognitive decline 147
Table 39. Omega-3 fatty acids and risk of cognitive decline – study characteristics and results from studies reviewed by Fotuhi et al., 2009 148
Table 40. Omega-3 fatty acids and risk of cognitive decline – recent cohort studies 150
Table 41. Intake of various types of fat and risk of cognitive decline....152
Table 42. Plasma selenium levels and risk of cognitive decline....154
Table 43. Intake of copper, zinc, and iron and risk of cognitive decline....156
Table 44. Mediterranean diet and risk of cognitive decline....158
Table 45. Intake of fruit and vegetables and risk of cognitive decline 160
Table 46. Diabetes mellitus and risk of cognitive decline 164
Table 47. Metabolic syndrome and risk of cognitive decline 168
Table 48. Hypertension and risk of cognitive decline 172
Table 49. Total cholesterol and risk of cognitive decline....181
Table 50. Homocysteine and risk of cognitive decline....183
Table 51. Obesity and risk of cognitive decline 186
Table 52. Depression and risk of cognitive decline 188
Table 53. Statins and risk of cognitive decline 193
Table 54. Antihypertensives and risk of cognitive decline....195
Table 55. NSAIDs and risk of cognitive decline 198
Table 56. Gonadal steroids and risk of cognitive decline....202
Table 57. Childhood factors and risk of cognitive decline 204
Table 58. Years of education and risk of cognitive decline....208
Table 59. Occupation and risk of cognitive decline 215
Table 60. Social engagement and risk of cognitive decline....220
Table 61. Cognitive activities and risk of cognitive decline....227
Table 62. Physical activity and risk of cognitive decline 231
Table 63. Leisure activities and risk of cognitive decline 238
Table 64. Smoking and risk of cognitive decline – results from studies reviewed by Anstey et al., 2007 241

Table 65. Tobacco use and risk of cognitive decline – recent cohort studies.....243
Table 66. Alcohol use and risk of cognitive decline – results from studies reviewed by Anstey et al., 2009 246
Table 67. Alcohol and risk of cognitive decline – recent cohort studies.....249
Table 68. APOE genotype and risk of cognitive decline.....255
Table 69. Therapeutic effects of gonadal steroids on development of AD 265
Table 70. Summary of evidence for association between nutritional factors and AD or cognitive decline 286
Table 71. Summary of evidence for association between medical factors and AD or cognitive decline 288
Table 72. Summary of evidence for association between medications and AD or cognitive decline 290
Table 73. Summary of evidence for association between social/economic/behavioral factors and AD or cognitive decline 293
Table 74. Summary of findings on potential risk factors and interventions for AD 308
Table 75. Summary of findings on potential risk factors and interventions for cognitive decline 309

Appendixes

Appendix A: Exact Search Strings
Appendix B: Evidence Tables
Appendix C: Quality Assessment – Systematic Reviews
Appendix D: Quality Assessment – Randomized Controlled Trials
Appendix E: Quality Assessment – Observational Studies
Appendix F: Peer Reviewers
Appendix G: List of Excluded Studies

Appendixes (including evidence tables) for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/alzheimers/alzcog.pdf.

Executive Summary

Introduction

Dementia is a loss of cognitive abilities in multiple domains that results in impairment in normal activities of daily living and loss of independence. Alzheimer's disease (AD) is the most common cause of dementia, responsible for 60 to 80 percent of all dementia. AD causes severe suffering for patients, including progressive functional impairment, loss of independence, emotional distress, and behavioral symptoms. Families and caregivers often experience emotional and financial stress.

The major risk factor for AD is age, with the prevalence doubling every 5 years after the age of 65. Most estimates of the prevalence of AD in the United States are about 2.3 million for individuals over age 70, but some estimates are as high as 5.3 million individuals over the age of 65. The number of individuals with mild cognitive impairment exceeds the number with AD. These individuals have mild impairment in cognition or daily functions that does not meet the threshold for a diagnosis of dementia, but they are at increased risk for development of AD, which makes them a prime target for intervention protocols.

Studies of selected risk or protective factors for cognitive decline and AD have been published, but it is not clear whether the results of these previous studies are of sufficient strength to warrant specific recommendations for behavioral, lifestyle, or pharmaceutical interventions/modifications targeted to these endpoints.

As background for an upcoming State-of-the-Science Conference in April 2010, the National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) commissioned this evidence report on "Preventing Alzheimer's Disease and Cognitive Decline" through the Agency for Healthcare Research and Quality (AHRQ). The aim is to summarize the available literature, frame the discussion regarding potential risk factors, and highlight the limitations of the evidence base.

We synthesized the existing literature on the following key questions:

Key Question 1: What factors are associated with the reduction of risk of Alzheimer's disease?

Key Question 2: What factors are associated with the reduction of risk of cognitive decline in older adults?

Key Question 3: What are the therapeutic and adverse effects of interventions to delay the onset of Alzheimer's disease? Are there differences in outcomes among identifiable subgroups?

Key Question 4: What are the therapeutic and adverse effects of interventions to improve or maintain cognitive ability or function? Are there differences in outcomes among identifiable subgroups?

Key Question 5: What are the relationships between the factors that affect Alzheimer's disease and the factors that affect cognitive decline?

Key Question 6: If recommendations for interventions cannot be made currently, what studies need to be done that could provide the quality and strength of evidence necessary to make such recommendations to individuals?

Methods

We searched MEDLINE® using Medical Subject Heading (MeSH) search terms, supplemented by keyword searches. In addition to MEDLINE®, we manually searched reference lists and searched the Cochrane Database of Systematic Reviews to identify relevant systematic reviews. For topics with a recent good-quality systematic review, we updated the search by identifying relevant primary literature published from 1 year prior to the search date of the review through October 27, 2009. When we did not identify a relevant good-quality review, we searched the primary literature for studies from 1984 through October 27, 2009. Because of the large volume of literature and the availability of specialized registries for genetic studies, we developed a separate search strategy for this topic and limited our review to select genes of special interest.

We restricted our review to human studies conducted in economically developed countries and published in English. We considered studies with participants ≥ 50 years old, of both sexes, all racial and ethnic populations, and drawn from general populations. We limited the sample size to ≥ 50 for randomized controlled trials (RCTs) and ≥ 300 for observational studies. We required at least 1 year between exposure and outcomes assessment for studies of cognitive decline, and 2 years for studies of AD. For Key Questions 1 and 2, we evaluated studies using observational designs; for Key Questions 3 and 4, we evaluated RCTs. Two reviewers independently assessed study eligibility and study quality and abstracted data. For Key Questions 1 through 5, we considered factors identified by the OMAR planning committee in five major categories: (1) nutritional factors; (2) medical factors (including medical conditions and prescription and non-prescription medications); (3) social/economic/behavioral factors; (4) toxic and environmental factors; and (5) genetics. Data were synthesized qualitatively and, when appropriate, using quantitative methods. We rated the overall level of evidence for each factor as high, moderate, or low using principles developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. The level of evidence is considered "high" when further research is very unlikely to change our confidence in the estimate of effect, and "low" when further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Results

A total of 25 systematic reviews and 250 primary studies met our inclusion criteria. The number of included studies differed markedly across the factors considered. Results are summarized immediately below by key question. We focus in this summary on the factors that showed an association with AD or cognitive decline. Those factors that did not show a consistent association with cognitive outcomes are described in more detail in the full report; this highlights

the point that among the many factors investigated, only a few have sufficient evidence to indicate a potential association with late-life cognitive outcomes.

Finally, at the conclusion of this section, we present two summary tables that show the direction of association (if any) and the level of evidence for all factors considered in the report.

Key Question 1 – Factors Associated with Risk of Developing AD

The results reported here are based on observational studies of AD, but to fully understand the associations between factors and cognitive outcomes, it is important to consider the results from both observational studies and RCTs when the latter are available.

In the nutrition category, both higher levels of folic acid and higher adherence to a Mediterranean diet were associated with a small to moderate decrease in risk of AD. The level of evidence was low for both of these factors.

For medical conditions, diabetes (summary odds ratio [OR] 1.39; 95 percent confidence interval [CI] 1.17 to 1.66), hyperlipidemia in mid-life, depression (summary OR 1.90; 1.55 to 2.33), and traumatic brain injury in males (summary OR 2.29; 1.47 to 3.58) were all associated with increased risk of AD. The level of evidence was low for each of these factors. No other factors showed a consistent relation to AD.

In the medication category, use of statins (summary hazard ratio [HR] 0.73; 95 percent CI 0.57 to 0.94) showed an association with decreased risk of AD. The observational studies for estrogen (summary relative risk [RR] 0.50; 95 percent CI 0.30 to 0.80) and antihypertensives showed a likely protective association with AD. The level of the evidence was low for these factors.

In the social, economic, and behavioral category, current smoking (summary RR 1.79; 95 percent CI 1.43 to 2.23) was associated with increased risk of AD. Moderate use of alcohol (summary RR 0.72; 0.61 to 0.86), more years of education, and higher levels of cognitive engagement showed an association with a moderately decreased risk of AD. Participation in physical leisure activity (summary HR 0.72; 95 percent CI 0.53 to 0.98) was generally associated with decreased risk of AD. Limited data on marriage and social support suggest that never being married and having less social support are associated with a moderately increased risk of AD. The level of evidence for all of these factors was low.

For the environmental exposure category, case-control studies were included for the subtopics reviewed (solvents, pesticides, lead, and aluminum) because there were few cohort studies that met inclusion criteria. Only pesticides showed a consistent and large association with higher risk of AD, but the level of the evidence was low.

For the review of genes, we identified 10 genes with the strongest and best quality evidence of an association with AD based on a systematic review and quality ratings conducted by ALZGene, an online database of genetic association studies performed on AD phenotypes. Based on the selection criteria, it is not surprising that all genes showed a significant association with AD. It is noteworthy that the epsilon 4 allele of the apolipoprotein E gene (APOE e4) allele showed the highest and most consistent risk for AD (summary OR 3.68; 95 percent CI 3.3 to 4.1). The level of evidence was moderate for the APOE e4 allele.

Key Question 2 – Factors Associated with Risk of Cognitive Decline

The results reported for this question are based on observational studies for cognitive decline.

Effect sizes in all cases were small to moderate. In the nutrition category, low plasma selenium showed an association with higher risk of cognitive decline. Higher amounts of vegetable intake, adherence to a Mediterranean diet, and higher levels of omega-3 fatty acids showed a likely association with decreased risk of cognitive decline, but evidence was limited for some of these factors. The level of evidence was low for all of these factors.

For the medical category, diabetes, metabolic syndrome, and depression showed fairly consistent associations with a small increased risk of cognitive decline. There were no studies that met inclusion criteria on cognitive decline and traumatic brain injury, sleep apnea, resiliency, or anxiety.

For the medication category, two types of medication (non-steroidal anti-inflammatory drugs [NSAIDs] and estrogen) showed possibly decreased risk for cognitive decline in select subgroups, but the other medications evaluated (statins, antihypertensives, and cholinesterase inhibitors) showed no association or no consistent association with cognitive decline.

Among the social, economic, and behavioral factors, smoking showed an increased risk of cognitive decline. Participation in non-physical/non-cognitive leisure activities, cognitive engagement, and physical activity all showed a fairly consistent protective association against cognitive decline. For observational studies, the level of evidence was low for these factors.

There were no eligible studies identified for the environmental exposure category.

In the genetic category, only APOE has been assessed in relation to cognitive decline. The studies fairly consistently report that APOE e4 is associated with greater cognitive decline on selected cognitive measures that were not consistent across studies. The level of evidence was rated as low for this factor.

Key Question 3 – Interventions to Delay the Onset of AD

There were relatively few RCTs assessing the association between the factors examined and AD. This is at least partially attributable to the fact that many of the factors are not amenable to testing in an RCT. There were also sparse, if any, data on differences in outcomes among subgroups because the few RCTs conducted have generally not been designed to assess such differences.

For the nutrition category, there was one RCT on vitamin E and one on gingko biloba that showed no association with AD. There were no other RCTs for nutritional factors, including folic acid and Mediterranean diet, factors suggested to decrease risk by observational studies.

The factors in the medical conditions category are not appropriate for randomization.

For the medications category, the three RCTs using antihypertensive medication showed no association with AD, but findings were limited by low power to detect a clinically important effect and assessment for all-cause dementia rather than AD. The eight RCTs using cholinesterase inhibitors showed no association with AD (moderate level of evidence). The two RCTs assessing NSAIDs showed increased risk of AD with rofecoxib, a medication that was subsequently withdrawn from the market for safety reasons, and increased risk for non-specific dementia with naproxen (HR 3.57; 95 percent CI 1.09 to 11.7) but the study was stopped early and findings were based on few cases. In intervention trials, estrogen alone showed no association, but estrogen combined with progesterone showed an increased risk of AD (HR 2.05;

95 percent CI 1.21 to 3.48). The level of evidence was rated as moderate for estrogen combined with progesterone and low for NSAIDs.

For the social, economic, and behavioral factors, there were no intervention trials for any factors, including physical activity and cognitive engagement, interventions suggested to be beneficial by observational studies.

Key Question 4 – Interventions to Improve or Maintain Cognitive Ability or Function

There were few RCTs assessing the effect of the various factors on cognitive decline. Additionally there was no information on differential outcomes by subgroups.

For the nutrition category, intervention trials of vitamin B6 and B12, vitamin E, and folic acid showed either no effect on cognitive decline or no consistent effect across trials. The level of evidence was judged to be high for vitamin E and moderate for the other supplements. We did not identify any trials that evaluated the Mediterranean diet or diets high in vegetables, practices that have been associated with lower risk of cognitive decline in observational studies.

The medical conditions were not appropriate for RCTs.

For the medication category, there was no effect of statins (level of evidence = high), antihypertensive medications (low), cholinesterase inhibitors (moderate), or estrogen (high). Some of the types of NSAIDs showed no effect, but one (naproxen) showed increased risk of cognitive decline. The level of evidence for NSAIDs was rated as low. Observational studies had suggested lower risk for both NSAIDs and estrogen.

For the social, economic, and behavioral categories, physical activity and cognitive training interventions showed a small protective association against cognitive decline. The level of the evidence for cognitive training was rated high, but that for physical activity was rated low.

Key Question 5 – Relationships Between Factors Affecting AD and Cognitive Decline

To address this question, we used the results from Key Questions 1 through 4 to compare the evidence for the effects of each exposure on risk of AD and cognitive decline. For factors with both RCT and observational evidence, we first compared the consistency of findings across study designs for each outcome. RCTs were preferred when of high quality. When studies showed a consistent effect on risk that was in the same direction for both AD and cognitive decline, we judged the results concordant. For many factors, the available data are quite limited, and concordant evidence across outcomes should not necessarily be interpreted as a robust finding. For other factors, not only were data limited but there was also marked heterogeneity in exposure or outcome measures across studies, so it was not possible to draw a conclusion about concordance. It is important to note that risk modification was generally small to moderate when factors were associated with AD (i.e., odds ratios and relative risk ratios were often substantially < 2.0). For cognitive decline, it is more difficult to determine the threshold for a meaningful change due to the numerous cognitive measures used to assess cognitive decline. But generally the differences in annual rate of decline between the exposed and unexposed groups were quite small.

To summarize results for Key Question 5, **factors showing an association for <u>both</u> AD and cognitive decline were:**

Increased risk:	Diabetes
	APOE e4
	Smoking
	Depression
Decreased risk:	Mediterranean diet (limited data)
	Cognitive engagement
	Physical activities

Key Question 6 – Future Research Needs

The current evidence is insufficient to recommend interventions. Weaknesses in the research methodology used in many of the studies reviewed have led to gaps in our knowledge. Critical improvements that are needed are: more precise, better validated, and more standard exposure measures; more standardized cognitive assessment measures across studies that are appropriate for the functional level of the sample (e.g. cognitively normal, mild cognitive impairment [MCI]); studies of longer duration; and better documentation and reporting of methods and results. Studies should also take into account the intensity, duration, and timing of the exposure, as exposures may be more influential and interventions more effective during critical or sensitive windows of time throughout life. Given the long sub-clinical, prodromal period of AD, RCTs need to continue for extended periods of time, and/or better methods need to be devised to evaluate potential interventions more rigorously in long-term observational studies. Although long-term RCTs are the ideal approach, in many cases the barriers to implementing such studies may make them unrealistic. For this reason, RCTs might aim to identify individuals at high risk of cognitive decline to make trials more efficient and economical. In addition, alternative research designs and analytical approaches should be considered. The development of research consortia might be considered to address the problems of inconsistent measurement of exposures and small sample sizes commonly found in previous research. Factors that may now be ready to be assessed further in RCTs are physical exercise and cognitive engagement. Although a few intervention trials have been done on some aspects of these factors, there is a need for trials that consider multiple components of the same general factor and multiple factors simultaneously.

Summary Tables

Tables ES1 and ES2 provide an overall summary of the direction of association (if any) and the level of evidence for all factors considered in the report for AD and cognitive decline, respectively.

Table ES1. Summary of findings on potential risk factors and interventions for AD

Direction of association	Factors	Level of evidence‡
Increased risk	• APOE e4 genotype • Conjugated equine estrogen with methyl progesterone*	Moderate
	• Some non-steroidal anti-inflammatory drugs* • Depressive disorder • Diabetes mellitus • Hyperlipidemia in mid-life • Traumatic brain injury in males • Pesticide exposure • Never married, less social support • Current tobacco use	Low
Decreased risk	• Mediterranean diet • Folic acid • HMG-CoA reductase inhibitors (statins) • Higher levels of education • Light to moderate alcohol intake • Cognitively engaging activities • Physical activity, particularly high levels	Low
No association	• Ginkgo biloba*	High
	• Vitamin E* • Cholinesterase inhibitors*	Moderate
	• Anti-hypertensive medication* • Conjugated equine estrogen • Omega-3 fatty acids* • Vitamins B12, C, beta-carotene • Homocysteine • Hypertension • Obesity • Metabolic syndrome • Early childhood factors • Occupational level • Lead	Low
Inadequate evidence to assess association	• Saturated fat intake • Fruit and vegetable intake • Trace metals • High caloric intake • Memantine • Sleep apnea • Anxiety disorders • Resiliency • Non-cognitive, non-physical leisure activities • Agent Orange, Gulf War Syndrome • Solvents, aluminum • Genetic factors other than APOE	(Not applicable)

* Data from observational studies and RCTs.
Abbreviations: APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; RCTs = randomized controlled trials
‡GRADE criteria (see Methods section)

Table ES2. Summary of findings on potential risk factors and interventions for cognitive decline

Direction of association	Factors	Level of evidence‡
Increased risk	• APOE e4 genotype • Low plasma selenium • Depressive disorder • Diabetes mellitus • Metabolic syndrome • Current tobacco use	Low
Decreased risk	• Cognitive training*	High
	• Vegetable intake • Mediterranean diet • Omega-3 fatty acids* • Physical activity* • Non-cognitive, non-physical leisure activities	Low
No association	• Vitamin C, Vitamin E, beta-carotene supplements* • Conjugated equine estrogen* • HMG-CoA reductase inhibitors (statins)*	High
	• Aspirin* • Dehydroepiandosterone* • Cholinesterase inhibitors* • Multivitamin supplement* • Vitamins B6, B12 and folic acid supplements*	Moderate
	• Alcohol intake • Non-steroidal anti-inflammatory drugs*† • Anti-hypertensive medication* • Homocysteine • Hyperlipidemia • Anxiety disorders • Hypertension • Obesity • Early childhood factors • Higher levels of education • Social network, social supports	Low
Inadequate evidence to assess association	• Trace metals • Fat intake • High caloric intake • Gingko biloba* • Memantine • Sleep apnea • Resiliency • Occupational level • Traumatic brain injury • Toxic environmental exposures • Agent Orange, Gulf War Syndrome • Genetic factors other than APOE	(Not applicable)

*Data from observational studies and RCTs.
† Not associated with decreased risk but may be associated with increased risk.
Abbreviations: APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; RCTs = randomized controlled trials
‡GRADE criteria (see Methods section)

Discussion and Conclusions

Many putative risk or protective factors for AD and cognitive decline have been proposed, but for few of them can any firm conclusions be drawn about their association with cognition in late life. It is important to note that some factors considered in this report that lack even moderate supporting evidence may, in fact, be associated with cognitive decline and AD; there simply was not sufficient evidence to draw such a conclusion. The main issues that preclude drawing conclusions are: few studies and thus limited evidence on any given factor; heterogeneity and imprecision in exposure and outcome measures, prohibiting thorough synthesis of the literature; inconsistent results among observational studies and between observational studies and RCTs; inconsistent results across the two outcomes of AD and cognitive decline; and when associations were found, the effect sizes were generally modest. Rigorous research methods addressing these issues will need to be developed to identify risk or protective factors with confidence, particularly with regard to the value of potential interventions.

A few of the factors on the list are ready for further investigation using RCTs. But although RCTs are the preferred source for investigating the effect of exposures, many of the factors on the list are not appropriate for intervention trials. This means that obtaining evidence on these factors is dependent on conducting well-designed observational studies. Adding further complexity to the issue, many of the exposures reviewed in this report likely do not work in isolation in their effect on risk of AD or cognitive decline; instead, they probably work in combination with other factors. Thus, for future research the ideal interventions should be multi-dimensional, combining interventions for multiple risk factors and controlling for many other factors.

Evidence Report

Chapter 1. Introduction

Scope of the Problem

Dementia is a loss of cognitive abilities in multiple domains that results in impairment in normal activities of daily living and loss of independence. There are a number of diseases that cause dementia, but the most common is Alzheimer's disease (AD), which is responsible for 60 to 80 percent of all dementia.[1] AD is a neurodegenerative disorder that begins in the mesial temporal lobe causing memory loss, but pathology soon spreads into other brain regions causing dementia. AD is defined pathologically by the presence of cerebral atrophy, extracellular amyloid plaques, and intraneuronal neurofibrillary tangles.

The major risk factor for AD is age, with the prevalence doubling every 5 years after the age of 65.[2] The prevalence of AD in 2002 was estimated to be 2.3 million individuals over age 70, based on a national population-based sample.[3] Another group estimated the prevalence of AD in 2000 at 4.5 million individuals aged 65 and older, based on a U.S. regional sample.[4] This latter figure was updated to an estimated 5.3 million individuals with AD in 2008.[1] This translates into about one in 8 to 10 persons over the age of 65 suffering from AD. The worldwide prevalence of dementia is estimated to be 35.6 million in 2010, with the number exceeding 65 million in 2030 and 115 million in 2050, making it a pressing global health concern.[5]

The diagnosis of AD is challenging both clinically and pathologically. There are multiple sets of well-established criteria for the clinical diagnosis of AD.[6-9] There is some variation among the sets of criteria, but each requires evidence of cognitive and functional decline that impacts the individual's ability to carry out routine daily activities. Even though significant progress has been made in identifying imaging, cerebrospinal fluid, and blood markers of disease, the diagnosis of AD during life currently is based primarily on the phenotypic presentation of cognitive and functional decline. However, the diagnosis of "definite AD" requires neuropathologic confirmation, which is complicated by the fact that AD-specific pathology infrequently occurs in isolation. Typically other pathology such as various types of vascular lesions or Lewy bodies are present, and these may increase with advancing age.[10] The presence of these multiple pathologies suggest that dementia is often due to multiple causes and not solely AD or any other single etiology. The correlation between AD pathology and cognitive symptoms is limited, providing further support for the idea that the other pathologies present also contribute to the cognitive presentation.

The term cognitive decline covers a continuum of cognitive changes, some of which are considered to be within the spectrum of normal aging and others that exceed expected decline for normal aging and are categorized as mild impairment. Typically performance in one or more cognitive domains such as memory, orientation, language, executive function, and praxis are assessed to determine decline. The diagnostic threshold between normal and pathological cognitive changes is imprecise. Pathological cognitive decline is often referred to as mild cognitive impairment (MCI) or cognitive impairment not demented (CIND); each term has multiple subtypes reflecting the construct of multiple etiologies. The diagnostic criteria for MCI and CIND are still evolving, but guidelines generally include greater than expected cognitive decline for the individual's age and education level, and no more than mild functional impairment insufficient to meet the threshold for a diagnosis of dementia.

The number of individuals with MCI or CIND exceeds that of AD. The prevalence of CIND in 2002 was estimated to be 5.33 million individuals over age 70 (22 percent), based on a nationally representative sample.[11] These individuals are at increased risk for development of AD, which makes them a prime target for intervention protocols. Longitudinal followup has shown that these individuals progress to dementia at a rate of 12 to 15 percent per year compared to 1 to 2 percent among cognitively healthy older adults.[11,12]

AD has a wide-ranging impact on individuals, families, and healthcare systems. It causes severe suffering for patients, including progressive functional impairment, loss of independence, emotional distress, and behavioral symptoms. Dementia is associated with a greater burden of co-existing medical illness,[13] nursing home placement,[14] and increased mortality.[15,16] Families and caregivers often experience emotional and financial stress. Up to 50 percent of caregivers suffer from significant psychological distress[17] and incur > $18,000 annually in unreimbursed caregiving expenses (in 1998 dollars).[18] In 2005, the direct cost to Medicare and Medicaid for care of people with AD and other dementias was $111 billion, and indirect costs to business for employees who were caregivers for individuals with AD and other dementia was estimated at $36.5 billion.[1] According to the World Alzheimer Report 2009,[5] AD accounts for 4.1 percent of all disability-adjusted life years (DALY) among those over 60, and cognitive impairment is the health condition that is most strongly associated with institutionalization.

AD is progressive, and it is the sixth leading cause of death for people of all ages in the United States.[19] Current therapies provide only modest symptomatic benefit, so methods to delay onset and/or modify progression are crucially needed.

Risk Factors for Alzheimer's Disease and Cognitive Decline

Findings from numerous epidemiological and clinical studies suggest that multiple biological, behavioral, social, and environmental factors may contribute to the delay or prevention of cognitive decline and AD. Studies of selected risk or protective factors for cognitive decline and AD have been published, but few systematic reviews have examined the quality of these studies and the conclusions that can be drawn from the data. It is not clear whether the results of these previous studies are of sufficient strength to warrant specific recommendations for behavioral, lifestyle, or pharmaceutical interventions/modifications targeted to these endpoints.

Researchers face several challenges in accurately identifying factors that alter the risk of cognitive decline and AD. The pathological changes for AD begin years prior to the overt clinical symptoms currently recognized as the hallmark of the disease,[20,21] suggesting that the relevant exposures may cover much of the lifespan. Some exposures may alter risk of later cognitive disease only at certain time points in life. For these factors, there may be a limited window of time when interventions will be effective. The quality of the measurement of exposures varies considerably across studies, and the effect of this is magnified when one considers the potential inter-relationship between many of the factors. The criterion standard procedures and criteria for the cognitive outcomes differ across studies. In addition, the domains assessed and the specific cognitive measures used differ across studies, making it difficult to synthesize findings from multiple sources. There is evidence that the effect of some putative risk factors (e.g., diabetes and psychological stress) may vary by subgroups such as race and/or

sex,[22,23] necessitating careful consideration of sample characteristics in the search for interventions. Finally, not all exposures under consideration are readily modified. Identifying the association between cognitive outcomes and all of the factors investigated in this report is the goal, but an added benefit would be realized by identifying those factors that can realistically be modified.

Purpose of this Evidence Report

The National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) reviews and evaluates clinically relevant NIH research program information and promotes the effective transfer of this information to the health care community. OMAR accomplishes this objective through its Consensus Development Program. This includes major Consensus Development Conferences and State-of-the-Science Conferences when less definitive evidence is available.

As background for a State-of-the-Science Conference scheduled for April 2010, OMAR and the National Institute on Aging commissioned this evidence report on "Preventing Alzheimer's Disease and Cognitive Decline" through the Agency for Healthcare Research and Quality (AHRQ). The key research questions were developed by a planning committee. The aim of the report is to summarize the available literature, frame the discussions regarding potential risk factors, highlight the limitations of the evidence base, and identify areas for future research. Through this report, OMAR seeks to increase the scientific rigor of its State-of-the-Science Conference. The focus of the this conference will be on evaluating existing data to determine whether there is sufficient quality of evidence to warrant any specific recommendations at this time for behavioral, lifestyle, or pharmaceutical interventions/modifications targeted at AD and cognitive decline in later life, and to identify needs for additional research.

The findings of our review clarify what is known about factors that modify the risk of AD or cognitive decline as a means of providing authoritative background information for participants at the State-of-the-Science Conference. More broadly, we expect that our findings will be useful to major stakeholders in this arena, including policymakers, advocacy groups, community organizations, health care providers, and mid- to late-life adults. We also identify future research priorities, which may be useful to government agencies and private sector funding organizations.

Role of the Technical Expert Panel

We identified experts in the field of Alzheimer's disease and cognitive decline to serve as members of the project's Technical Expert Panel (TEP). The TEP contributes to AHRQ's broader goals of (1) creating and maintaining science partnerships and public-private partnerships; and (2) meeting the needs of an array of potential customers and users of this product. To ensure accountability and scientifically relevant work, we asked the TEP for advice at key stages of the project. More specifically, TEP members participated in conference calls and email exchanges to refine the analytic framework and key questions at the beginning of the project, refine the scope of the project, discuss inclusion and exclusion criteria, and provide expert advice on methodology.

Members of the TEP were:

- Jesse A. Berlin, Sc.D. – Research & Development at Johnson & Johnson Pharmaceuticals
- Ornit Chiba-Falek, Ph.D. – Duke University
- John Ioannidis, M.D. – University of Ioannina, Greece
- Dan Kaufer, M.D. – University of North Carolina, Chapel Hill
- Michael Marsiske, Ph.D. – University of Florida

These individuals represent a broad range of specialties relevant to our topic (including neurology, psychology, statistics, and genetics). Because of their extensive knowledge of the literature on these topics, TEP members were also invited to participate in the peer review of this draft report.

Organization of this Report

Chapter 2 describes the methods used to produce this report, including the key questions addressed, the analytic framework, our search strategies, and inclusion/exclusion criteria. In Chapter 3, we report on the numbers of publications reviewed and present the results of our literature search and synthesis on the six key questions that OMAR posed for this review. Chapter 4 discusses these findings further, highlights methodological shortcomings of the extant research, and offers recommendations for future research. Chapter 5 summarizes the major conclusions.

Chapter 2. Methods

Introduction

In this chapter, we document the procedures used by the Duke Evidence-based Practice Center (EPC) to develop this comprehensive evidence report on the factors associated with Alzheimer's disease (AD) and cognitive decline. To provide a context for the review, we first present the key questions and analytic framework. Next we describe the methods used to identify articles relevant to our key questions, our inclusion/exclusion criteria, and the process we used to abstract relevant information from eligible articles and generate our evidence tables. We discuss our criteria for evaluating the quality of individual articles and synthesizing the evidence. Finally, we describe the peer review process.

Key Questions

This report addresses risk factors and potential therapeutic interventions that may modify the risk of AD or cognitive decline. A National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) State-of-the Science Conference planning committee developed the key questions and specified the populations and factors to be evaluated. The specific factors and interventions to be reviewed were refined with input from members of the project's technical expert panel (TEP), representatives of NIH-OMAR, and staff at the Agency for Healthcare Research and Quality (AHRQ). Although a large number of factors are considered, the report is not inclusive of all factors that have been associated with AD or cognitive decline.

The key questions considered are:

Key Question 1: What factors are associated with the reduction of risk of Alzheimer's disease?

Key Question 2: What factors are associated with the reduction of risk of cognitive decline in older adults?

Key Question 3: What are the therapeutic and adverse effects of interventions to delay the onset of Alzheimer's disease? Are there differences in outcomes among identifiable subgroups?

Key Question 4: What are the therapeutic and adverse effects of interventions to improve or maintain cognitive ability or function? Are there differences in outcomes among identifiable subgroups?

Key Question 5: What are the relationships between the factors that affect Alzheimer's disease and the factors that affect cognitive decline?

Key Question 6: If recommendations for interventions cannot be made currently, what studies need to be done that could provide the quality and strength of evidence necessary to make such recommendations to individuals?

For all questions, we were interested in adults age 50 or older drawn from general populations. For Key Questions 1 and 2, we examine all the risk factors from an epidemiologic standpoint, limiting our review to observational studies and focusing on factors that are not amenable to randomization (e.g., hypertension). For Key Questions 3 and 4, we prioritized randomized controlled trials (RCTs), but because the evidence was often sparse or limited to select samples, we supplemented trial data with evidence from observational studies, where necessary. For Key Question 5, we were interested in the consistency of findings for each exposure/intervention on risk of AD and cognitive decline.

The exposures/interventions evaluated are listed in Table 1.

Table 1. Exposures/interventions evaluated in this report

Factors examined for Key Questions 1, 2, and 5	**Factors and interventions examined for Key Questions 1, 2, 3, 4, and 5**
Medical: A. Vascular factors: Diabetes mellitus Metabolic syndrome Hypertension Hyperlipidemia Homocysteine B. Other medical factors Sleep apnea Obesity Traumatic brain injury C. Psychological and emotional health Depression Anxiety Resiliency ***Social/economic/behavioral:*** A. Early childhood factors (e.g., early life environment, rural/urban upbringing) B. Education/occupation/IQ/intelligence C. Tobacco/nicotine use D. Alcohol use ***Toxic environmental exposures,*** including pesticides, pollution, Gulf War Syndrome, and Agent Orange exposure ***Genetics***	***Nutritional and dietary factors:*** A. B vitamins and folate B. Other vitamins C. Gingko biloba D. Omega-3 fatty acids E. Other fats F. Trace metals G. Mediterranean diet H. Fruit and vegetable intake I. Total intake of calories, carbohydrates, fats, and proteins ***Prescription and nonprescription drugs:*** A. Statins B. Antihypertensives C. Anti-inflammatories D. Gonadal steroids E. Cholinesterase inhibitors F. Memantine ***Social/economic/behavioral factors:*** A. Social engagement (social network size, social support, and marital status) B. Cognitive engagement (including games, puzzles, and cognitive training) C. Physical activities D. Other (non-cognitive, non-physical) leisure activities

Analytic Framework

Our analytic framework (Figure 1) describes the progression from normal cognition to the initiation of subclinical pathophysiological processes to cognitive decline that is beyond what is expected for normal aging and to AD. Although there is a potential for primary prevention prior to the initiation of pathophysiological processes leading to cognitive decline, there are currently not well-validated methods to measure these processes in the absence of cognitive decline. Therefore, we did not consider effects of the candidate factors on changes in pathophysiological processes. The figure shows the potential for treatment interventions to effect cognitive decline and the risk for AD.

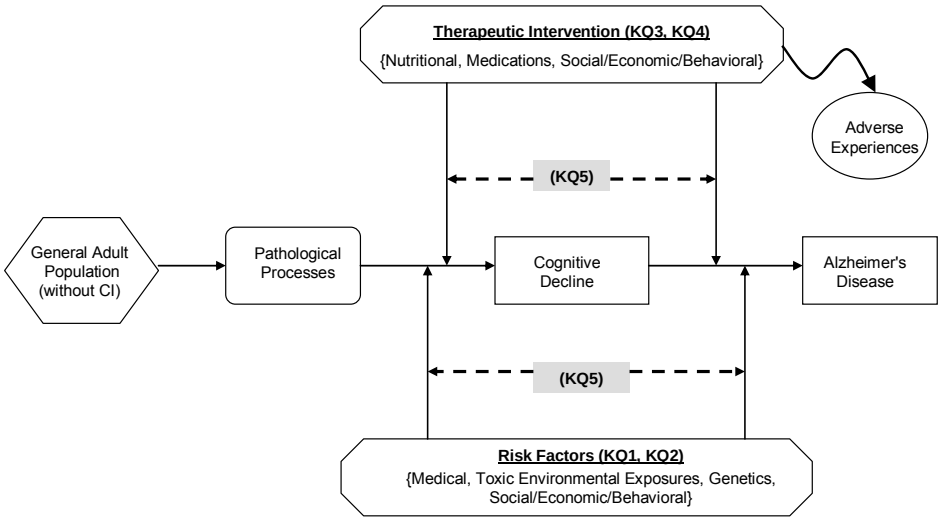

Figure 1. Analytic framework

Literature Review Methods

Inclusion/Exclusion Criteria

After discussion with the TEP, we generated a list of article inclusion and exclusion criteria (Table 2) for the Key Questions. Because of the large number of factors and interventions to review, we searched initially for good quality systematic reviews. We included primary literature to update eligible reviews or when good quality reviews were unavailable. We limited the primary literature to comparative studies published in English that enrolled adults age 50 years or older at the time of final cognitive assessment, drawn from general populations in economically developed countries. We defined general populations as those drawn primarily from non-institutionalized community settings or general medical populations. With three exceptions, we

limited observational studies to longitudinal designs where the risk factor or intervention was measured prior to the outcome. We made exceptions for traumatic brain injury and toxic/environmental exposures because of the difficulties studying these factors longitudinally, and for sleep apnea, because of the absence of cohort studies. Because AD is a relatively uncommon event, we required a sample size greater than 300 to focus on studies with higher statistical power. For similar reasons, we required at least 1 year between exposure and outcomes assessment for studies of cognitive decline, and at least 2 years for studies of AD.

Table 2. Inclusion and exclusion criteria

Category	Criteria
Study population	Humans, all races, ethnicities, and cultural groups KQ 1-6: Adults age ≥ 50 years old; drawn from a general population or general medical setting, with normal cognition or mild cognitive impairment
Study geography	Developed countries: United States, Canada, United Kingdom, Western Europe, Australia, New Zealand, Hong Kong, Japan, Republic of China (Taiwan), Singapore, South Korea, Israel
Factors/interventions	*See* Table 1, above
Study outcomes	KQ1 & 3: Diagnosis of Alzheimer's disease using an acceptable standard (e.g., National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Criteria) KQ2 & 4: Diagnosis of mild cognitive impairment using an acceptable standard (e.g., Petersen's criteria) or change in cognition using at least two measurements on an acceptable measure
Outcome timing	KQ1 & 3: At least 1 year after the exposure or intervention KQ2 & 4: At least 2 years after the exposure or intervention
Time period	1984 to October 27, 2009
Publication languages	English only
Admissible evidence (study design and other criteria)	Good quality systematic reviews that addressed a question of interest and used eligibility criteria consistent with our inclusion/exclusion criteria Original research studies that provide sufficient detail regarding methods and results to enable use of the data and results; relevant outcomes must be able to be abstracted from data presented in the papers. If risk for non-specific dementia only were reported, we required ≥ 60% of the outcomes to be AD. Eligible original research designs include: KQ 3 & 4: Randomized controlled trials (RCTs); KQ 1-4: Observational studies: longitudinal designs comparing exposed to unexposed. For TBI, sleep apnea, and toxic environmental, case-control studies were also eligible. Sample sizes must be appropriate for the study question: RCTs ≥ 50; longitudinal observational ≥ 300

Abbreviations: AD = Alzheimer's disease; KQ = key question; RCT = randomized controlled trial; TBI = traumatic brain injury

Literature Search Strategies

Based on the above-described inclusion/exclusion criteria, we generated a list of Medical Subject Heading (MeSH) search terms, supplemented by keyword searches, to search MEDLINE®. Search terms and strategies were developed in consultation with a medical

librarian. The exact search strategies used are given in Appendix A.[*] In addition to MEDLINE®, we searched the Cochrane Database of Systematic Reviews to identify relevant systematic reviews. For topics with a recent good quality systematic review (*see* "Assessment of Methodological Quality," below), we updated the search by identifying relevant primary literature published from 1 year prior to the search date through October 27, 2009. The 1-year overlap is necessary because of delays between publication in journals and availability for searching in MEDLINE®. Relevant older literature missed or excluded in prior reviews that was relevant and met eligibility criteria was included.

When we did not identify a relevant good quality review, we searched the primary literature to include studies from 1984 through October 27, 2009. Electronic searching was supplemented by examining the bibliographies of reviews and primary studies. Because of the large volume of literature and availability of specialized registries for genetic studies, we developed a separate search strategy for this literature. We examined the HUGE and ALZGene databases to identify relevant systematic reviews for genes identified as being of special interest in consultation with the TEP.

Using the pre-specified inclusion/exclusion criteria, titles/abstracts were examined independently by two reviewers for potential relevance to the key questions. Articles included by either reviewer underwent full-text screening. At the full-text screening stage, two independent reviewers read each article to determine if it met eligibility criteria. Disagreements were resolved by consensus. At the full-text review stage, simple agreement was 84 percent, and median chance corrected agreement was kappa = 0.63 (range 0.40 to 1.0). Articles meeting our eligibility criteria were included for data abstraction.

Data Abstraction and Data Management

Data from published reports were abstracted into evidence tables by one reviewer and over-read by a second reviewer. Data elements abstracted included descriptors to assess applicability, quality elements, intervention/exposure details, and outcomes. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion when consensus could not be reached. The final evidence tables are intended to provide sufficient information so that readers can understand the study and determine its quality. Evidence tables for all included studies are presented in Appendix B. Because some studies address more than one exposure or question, the evidence tables are organized alphabetically by author.

Assessment of Methodological Quality

We developed separate criteria for assessing the methodological quality of included systematic reviews, RCTs, and observational studies. These criteria are given in Appendices C, D, and E, respectively. Briefly, for systematic reviews we assessed the comprehensiveness of the search strategy, the description and appropriateness of inclusion criteria, whether primary studies were assessed for quality and the adequacy of the quality measure, the reproducibility of methods to assess studies, whether the results of relevant studies were combined appropriately,

[*] Appendixes (including Evidence Tables) for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/alzheimers/alzcog.pdf.

whether heterogeneity and publication bias were assessed, and whether the conclusions were supported by the data presented.

For RCTs, we used the key criteria described in the AHRQ methods manual for Comparative Effectiveness Reviews,[24] adapted to this specific topic. These criteria are: adequacy of randomization and allocation concealment; the comparability of groups at baseline; blinding; the completeness of followup and differential loss to followup; whether incomplete data were addressed appropriately; the validity of outcome measures; and conflict of interest.

To assess individual observational studies, we adapted a basic set of quality criteria used in previous AHRQ evidence reports.[25,26] These criteria concern the methods used to select the cohort, the adequacy of the sample size, the methods used to ascertain exposure status and outcomes, the adequacy and completeness of followup, and the appropriateness of the analytic methods used. Abstractors assigned a rating of "yes," "partially," "no," or "can't tell" to each item and provided a brief rationale for their decisions. We did not attempt to assign a summary quality score ("A, B, C" or "Good, Fair, Poor") to individual RCTs or observational studies because there is no evidence that the use of any particular quality scoring system has a substantial impact on the results of systematic reviews.[27] In addition, our experience has been that it is more helpful to identify consistent and specific quality issues that affect the majority of the included studies (concerning, e.g., sample size, analytic methods, or ascertainment bias) in order to guide future research, rather than relying on a global quality score.

We used principles from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (www.gradeworkinggroup.org) to summarize the level of evidence for each factor as low, moderate, or high. The GRADE approach was developed to evaluate the overall level of evidence for interventions, but we have extended the approach to factors (e.g., medical illness) that would not be considered as interventions. The approach considers the body of evidence for each outcome, assigning an initial rating of low quality to observational studies and high quality to RCTs. These initial ratings may be modified by the following factors: detailed study design, consistency, strength of association, dose-response effect, directness, precision, and if all plausible confounding would reduce a demonstrated effect. The resulting judgments about the level of evidence are presented separately in summary tables for AD and cognitive decline in Chapter 5. Judgments about the strength of evidence were made by at least two investigators; final ratings were reached by consensus.

Data Synthesis

When good quality systematic reviews were identified, we summarize the findings in narrative form in Chapter 3 ("Results"). Any new studies identified since the systematic review was published are summarized descriptively in a table that includes the study sample, exposure classification, duration of followup, adjustment for confounding, and primary outcomes. We evaluated whether the new evidence was likely to change estimates from the prior review by considering the precision and stability of estimates from the original review, the number and size of the new studies relative to studies in the original review, the quality of the new studies, and the consistency in estimates and conclusions between the new evidence and the original review. After considering these issues, we updated prior meta-analyses when substantial new evidence was available and a new summary estimate was likely to lead to different conclusions. We performed primary meta-analysis when studies were conceptually homogeneous and the needed data were available for the summary estimate. Since meta-analysis of observational studies may

give spurious precision,[28] we applied meta-analysis to observational data only when studies were high quality and conceptually homogeneous (similar subjects, exposure, outcomes).

Synthesizing studies that evaluated cognitive decline was particularly challenging. Cognitive decline can be classified categorically by meeting proposed criteria such as those for mild cognitive impairment (MCI), or by exceeding a threshold on a global cognitive measure such as the Mini-Mental State Examination (MMSE). These categorical outcomes are often more clinically meaningful and therefore were prioritized in this review. Cognitive decline may also be examined using continuous measures of global, isolated, domain-specific measures (e.g., memory, processing speed), or composites of multiple measures for a domain. Many of these measures have not been demonstrated to be responsive to change, and any changes observed may be of uncertain clinical significance. Because of the heterogeneity of the continuous measures reported and the large scope of the present review, we evaluated the relevance of studies reporting continuous measures for each exposure. When there were adequate numbers of studies using categorical outcomes to address the question, we did not provide detailed summaries of the studies reporting continuous outcomes.

Peer Review Process

Among the more important activities involved in producing a credible evidence report is conducting an unbiased and broadly based peer review of the draft report. External reviewers for this report included clinicians and representatives of professional societies, as well as members of the TEP. The list of nominees was forwarded to AHRQ for vetting and approval. A list of peer reviewers submitting comments on this draft is included in Appendix F.

Chapter 3. Results

Literature Search Results

Figure 2 summarizes the results of our literature search and screening process. We identified a total of 6713 citations from the electronic search and an additional 194 citations from other sources. After applying inclusion/exclusion criteria at the title-and-abstract level, 1626 full-text articles were retrieved and screened. Of these, we excluded 1035 that did not meet our inclusion criteria. Appendix G* provides a complete listing of articles excluded at the full-text stage, with reasons for exclusion.

After applying quality assessment criteria to the systematic reviews captured in our search, we identified 25 good quality reviews (Table 3), which are summarized in the relevant sections below. Publications that were included in one of these 25 reviews are not generally counted in our tally of original research studies. However, some original research publications may have addressed more than one factor, and may be included in both an existing systematic review for one factor, and as an original research study for another factor. In the end, we included 250 original research studies, along with the 25 systematic reviews.

* Appendixes (including Evidence Tables) for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/alzheimers/alzcog.pdf.

Figure 2. Literature flow diagram

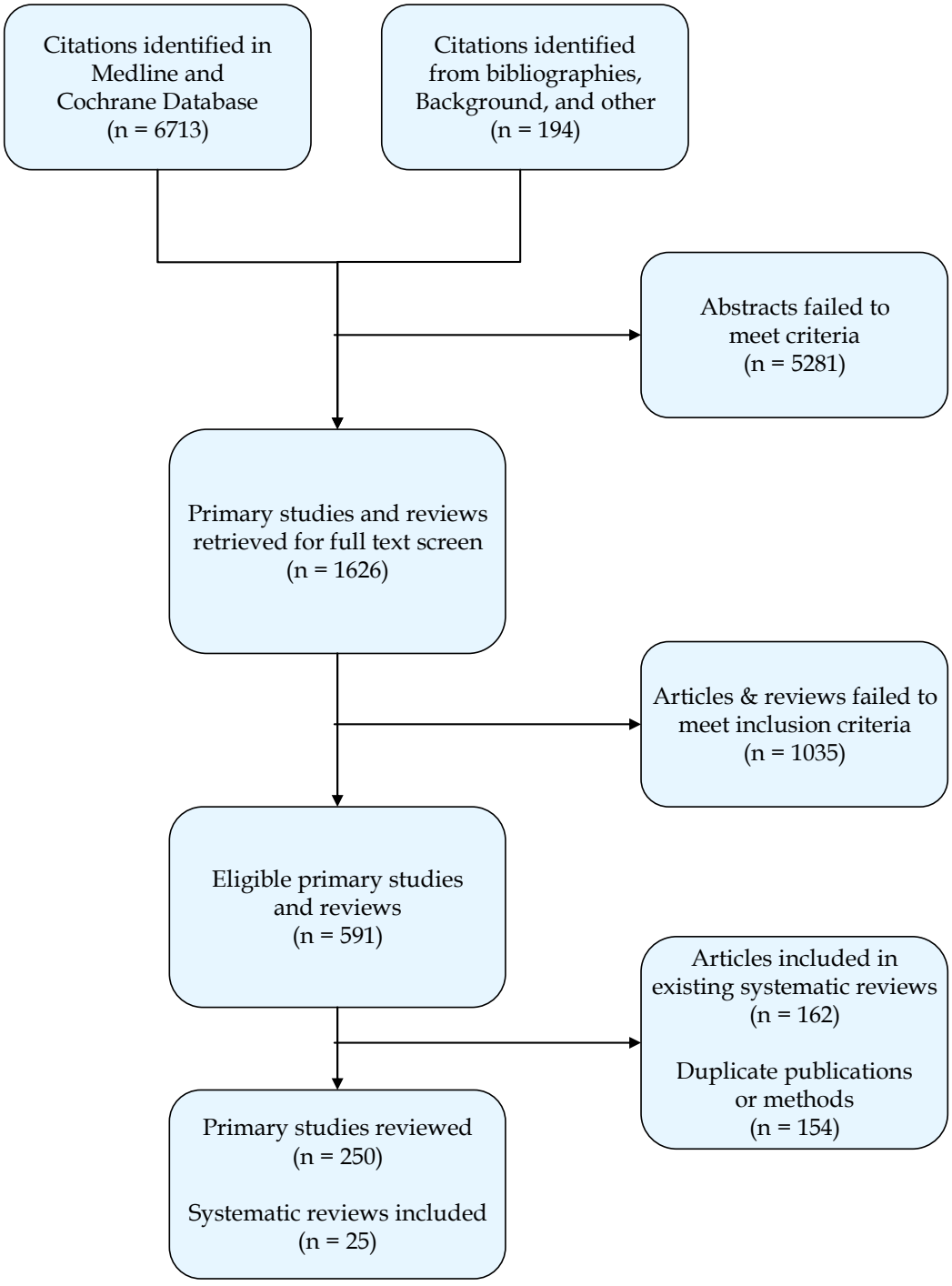

Table 3. Included systematic reviews

Author, Year	Exposure	OUTCOMES		Types of Studies Reviewed
		Alzheimer's Disease	Cognitive Decline	
I) Nutrition/Dietary				
Fotuhi et al., 2009[29]	Omega 3	Yes	Yes	RCTs and observational (cohort)
Issa et al., 2006[30]	Omega 3	Yes	Yes	Observational (cohort)
Lim et al., 2006[31]	Omega 3	Yes	No	RCTs
Balk et al., 2006[32]	Vitamin B and berries	Yes	Yes	RCTs and observational (cohort) in human, animal, & in vitro
II) Medical				
McGuiness et al., 2009[33]	Statins	No	Yes	RCTs
McGuiness et al., 2006[34]	Antihypertensives	Yes	Yes	RCTs
Szekely et al., 2004[35]	Anti-inflammatory	Yes	No	Observational
Grimley Evans et al., 2006[36]	Gonadal steroids	No	Yes	RCTs
Lethaby et al., 2008[37]	Gonadal steroids	No	Yes	RCTs
LeBlanc et al., 2001[38]	Gonadal steroids	Yes	Yes	Observational (case-controlled and cohort)
Nickelsen et al., 1999[39]	Gonadal steroids	No	Yes	RCTs
Anstey et al., 2008[40]	Hypercholesterolemia	Yes	Yes	Observational (prospective cohort)
Biessels et al., 2006[41]	Diabetes mellitus	Yes	No	Observational
Lu et al., 2009[42]	Diabetes mellitus	Yes	Yes	Observational
Cukierman et al., 2005[43]	Diabetes mellitus	No	Yes	Observational
Raschetti et al., 2007[44]	Cholinesterase	Yes	Yes	RCTs
Ownby et al., 2006[45]	Depression	Yes	No	Observational (cohort)
Fleminger et al., 2003[46]	Traumatic brain injury	Yes	No	Observational (case-controlled)
Beydoun et al., 2008[47]	Obesity	Yes	No	Observational (cohort)
III) Social/Economic/Behavioral				
Angevaren et al., 2008[48]	Physical activity	No	Yes	RCTs

Author, Year	Exposure	OUTCOMES		Types of Studies Reviewed
		Alzheimer's Disease	Cognitive Decline	
Caamano-Isoma et al., 2006[49]	Education	Yes	No	Observational
Anstey et al., 2007[50]	Tobacco	Yes	Yes	Observational (prospective cohort)
Anstey et al., 2009[51]	Alcohol	Yes	Yes	Observational
IV) Environmental				
Santibanez et al., 2007[52]	Toxic exposures	Yes	No	Observational (case-controlled & cohort)
V) Genetics				
Bertram et al., 2007[53]	Genetic factors	Yes	No	Gene association

Abbreviations: RCTs = randomized controlled trials

Measurement of Cognitive Outcomes

Alzheimer's Disease and Dementia

The assessment for dementia was similar across most of the major cohort studies we identified. Typically the cognitive batteries used included measures of global cognitive function; language (naming and verbal fluency); verbal memory (word list and/or paragraph immediate and delayed recall); visual memory; executive function and processing speed; attention; and an estimate of baseline intelligence or reading ability. The specific tests used differed across the studies, but the cognitive domains assessed were generally similar. The studies differed in their use of information from a proxy informant in the diagnostic process; that is, some studies used information from informants, while others did not.

Cognitive Decline

Cognitive decline was measured in a number of different ways in the included studies. Some studies used a diagnosis of incident mild cognitive decline (MCI) or cognitive impairment not demented (CIND) as the definition for cognitive decline. The criteria used for these diagnostic categories varied across studies, but typically included a psychometrically determined mild impairment on memory tests and/or other cognitive domains, with at most mild functional impairment in daily activities.

Other studies defined cognitive decline based on longitudinal change on one or more cognitive measures. Some studies determined decline on the test(s) based on continuous change in the test score over time, while other studies defined decline in categorical (often dichotomous) terms based on a predetermined threshold of change in performance over two or more time points.

Review of the studies included in this systematic review found that about 40 percent reporting on cognitive decline based their findings on performance on a single cognitive measure, typically a general measure of cognitive function. The most common measures used were the Mini-Mental State Examination (MMSE) or an abbreviated form of the MMSE, the Modified Min-Mental State Examination (3MS), and some form of the Telephone Interview for Cognitive Status (TICS). Approximately half of the studies using these measures defined cognitive change as a continuous outcome, while the other half defined cognitive change in categorical terms. Some studies reported results for only a single measure, such as a verbal memory task, from the battery of tests that were administered.

Another 40 percent of the included studies assessed cognitive decline using multiple neuropsychological measures. The majority of these studies measured decline as a continuous outcome. Some of these studies reported results for both the individual cognitive measures and a global composite measure combining all tests. The specific cognitive tests used varied across studies but typically included tests in a number of the following domains: global cognitive function (MMSE, 3MS, TICS); verbal memory (word list or paragraph immediate and delayed recall); visual memory; verbal fluency; naming; speed of processing; attention; executive function; working memory; and reasoning.

Finally, about 10 percent of included studies defined cognitive decline based on a composite global index of performance on all tests combined. Some of these studies presented the results as a continuous outcome, while others reported them as a categorical outcome.

Key Question 1 – Factors Associated with Reduction of Risk of Alzheimer's Disease

Key Question 1 is: What factors are associated with the reduction of risk of Alzheimer's disease?

Nutritional and Dietary Factors

B vitamins and folate. We identified one good quality systematic review that examined the association between B vitamins or berries and development of Alzheimer's disease (AD).[32] However, we decided not to provide a detailed summary of this review here because the majority of the studies identified in the review did not meet our eligibility criteria, and the review authors did not conduct any meta-analysis combining the studies, thus providing limited benefit for our purpose. Instead, we here review the studies identified by the review that met our eligibility criteria, along with additional studies identified in our literature search. We identified a total of five eligible cohort studies in this way.[54-58] These studies are summarized in Table 4; detailed evidence tables are provided in Appendix B. Three studies used samples from U.S. communities,[54-56] and two from communities in Europe.[57,58] Length of followup across the studies ranged from an average of approximately 3.0 to 6.1 years. In all five studies, participants were non-demented at baseline. Two of the studies used blood serum levels of various B vitamins and folate.[57,58] The other three[54-56] estimated levels of B vitamins and folate based on self-reported responses on nutrition questionnaires. The studies that used blood serum levels to characterize exposure used standard methods to determine the levels of folate and B vitamins. Another research group that reported on two different samples[55,56] has published the results of analyses assessing the reliability and validity of the food frequency questionnaires used in their studies.[59] They reported that the Spearman correlations for 1-year reproducibility of responses to the questionnaire were 0.70 for total folate, 0.50 for total vitamin B-12, and 0.58 for vitamin B-6. The Pearson correlations for validity were 0.50 for total folate, 0.38 for total vitamin B-12, and 0.51 for total vitamin B-6. The authors also reported that the performance characteristics did not differ significantly by cognitive ability.

All of the studies used sample selection methods to minimize selection bias. Four studies compared some baseline characteristics by exposure level.[55-58] All studies used standard criteria for the diagnosis of AD, but only two used an informant report as part of the diagnostic process.[57,58] Only some of the studies reported results for AD cases only, but the studies that reported results for dementia as a whole included enough AD cases to meet our eligibility criteria. Two studies explicitly stated that the dementia diagnosis was assigned blind to the exposure level of B vitamins and folate;[55,56] however, it is unlikely that details of B vitamin and folate exposure were discussed during the diagnostic process in any of the studies. Analyses were appropriate and generally controlled for relevant potential confounders.

Results from the two studies[57,58] that measured folate serum levels showed that low baseline folate levels were consistently associated with increased risk of AD (or dementia). In

comparison, B12 levels were typically not associated with risk of AD. The three studies that used estimated dietary intake of folate and B vitamins based on self-reported information reported conflicting results. One reported an association between higher intake of folate and reduced risk of AD,[54] while another did not find a significant reduction in AD risk associated with folate intake.[55] Neither study found an association between vitamins B6 or B12 and risk of AD. Direct comparisons of the two studies to identify reasons for these inconsistent results are difficult, but based on the information provided in the studies, the average rate of folate intake may differ between the two studies, with the study by Morris and colleagues[55] reporting a lower rate of folate intake. Only one study examined niacin (B3) intake and found a lower risk for AD associated with higher intake of niacin.[56]

In conclusion, based on folate levels measured in serum, there is preliminary evidence from two studies that low folate levels are associated with increased risk of AD. The two studies estimating folate level from self-report dietary information did not find a consistent association with risk of AD. The evidence does not suggest an association between B12 and risk of AD. The one study assessing estimated niacin intake showed an association between higher niacin intake and lower risk of AD; confirmation of this is required prior to drawing conclusions. Further confirmation is also needed of the putative association between folate serum levels and risk of AD.

Table 4. B vitamins and folate and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Ravaglia et al., 2005[57]	Community cohort (720)	3.8 years (SD 0.8)	Serum levels of vitamin B12 and folate Plasma levels of homocysteine	NINCDS-ADRDA	Age Sex Education APOE Stroke Creatinine Smoking Diabetes Hypertension Cardiovascular disease BMI Other markers (folate, vitamin B12, and homocysteine)	After adjustment for homocysteine and other covariates, low folate concentrations (< 11.8 nmol/L) were independently related to AD risk (1.98; 95% CI 1.15 to 3.40; P = 0.014). Compared with the top folate quartile, the adjusted HRs for AD were 2.04 (1.02 to 4.09; P = 0.045) for the bottom folate quartile, 1.30 (0.62 to 2.72; P = 0.484) for the lower second, and 0.66 (0.29, 1.54; P = 0.340) for the third (P for trend = 0.015). By contrast, adjusted HRs relating low vitamin B12 concentrations to risk of developing AD (0.66; 0.40 to 1.09; P = 0.103) were not statistically significant.
Wang et al., 2001[58]	Community cohort (370)	3 years 60 AD cases	Serum B12 and folate levels	DSM	Age Sex Education level Baseline cognitive score Hemoglobin levels Alcohol consumption Cardiovascular disease	HRs for risk of incident AD during the 3-year followup after adjusting for age, sex and education: B12 ≤ 150 vs. ≥ 150 pmol/L: 1.6 (95% CI 0.9 to 2.8) Folate ≤ 10 vs. ≥ 10 nmol/L: 1.7 (1.0 to 3.4) Both low B12 and low folate: 2.1 (1.4 to 3.8) When low levels were defined as B12 ≤ 250 pmol/L and folate ≤ 12 nmol/L, the adjusted RR for AD was 7.0 (95% CI 5 1.6 to 31.6) in subjects with MMSE score > 26 and was 1.4 (5 0.7 to 2.7) in subjects with MMSE score ≤ 26. Low levels of vitamin B12 or folate after controlling for age, sex, education, and baseline cognitive functioning: HR 1.4 (95% CI 0.8 to 2.4)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Luchsinger et al., 2007[54]	Community cohort (965)	6.1 (SD 3.3) years 192 AD cases	Daily dietary, supplement and total intake of folate and vitamins B6 and B12 estimated from self-reported responses semi-quantitative food frequency questionnaire	NINCDS-ADRDA DSM	Age Race Sex Educational level APOE DM HTN Smoking Heart disease Stroke	The risk of AD decreased with the increasing quartile of total folate intake, and this association was statistically significant (p for trend = 0.02) after adjustment for intake of vitamins B6 and B12. Adjusted HR for the highest quartile (≥ 487.9 micrograms) of total folate intake compared to the lowest quartile was 0.5 (95% CI 0.3 to 0.9). Association between dietary folate intake and AD was not statistically significant; adjusted HR for the fourth quartile of dietary folate intake was 0.8 (0.5 to 1.2; P = 0.25 for trend). Total intakes of vitamin B6 and B12 were not related to the risk of AD in any of the models.
Morris et al., 2006[55]	Community cohort (1041)	3.9 years 162 AD cases	Estimates of total intake of folate and vitamins B6 and B12 during the previous year were calculated from self-report responses on a modified Harvard food frequency questionnaire	NINCDS-ADRDA	Age Race Sex Educational level Period of observation APOE Vitamin E Niacin	Using nutrient-adjusted models comparing highest quintile to lowest quintile: Neither total folate (OR 1.6; 95% CI 0.5 to 5.2) or folate from food (1.8; 0.8 to 4.1) was associated with risk of AD. Neither total vitamin B12 (0.6; 0.2 to 1.6) nor vitamin B12 from food (1.0; 0.3 to 2.7) was associated with risk of AD. Neither total vitamin B6 (0.7; 0.2 to 2.4) nor vitamin B6 from food (0.7; 0.3 to 1.4) was associated with risk of AD. Results for intake of folate, vitamins B6 and B12 from food only were not associated with risk of AD either.
Morris et al., 2004[56]	Community cohort (815)	3.9 years 131 AD cases	Estimates of total intake of niacin (B3) during the previous year were calculated from self-report responses on a modified Harvard food frequency questionnaire	NINCDS-ADRDA	Age Race Sex Educational level APOE Time interval between assessments Sample weights Vitamin E	Reduction in AD risk based on adjusted ORs for highest quintile compared to lowest quintile: Total niacin: OR 0.2 (95% CI 0.01 to 0.7; p for trend = 0.04) Niacin from food: OR 0.3 (0.1 to 0.7; p for trend = 0.006) Tryptophan (niacin dietary precursor): OR 0.4 (0.1 to 0.8; p for trend = 0.03) Niacin equivalents: OR 0.2 (0.1 to 0.8; p for

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
					Vitamin C Beta-carotene Multiple vitamin use DM HTN Smoking Alcohol use Stroke Heart disease Folate	trend = 0.01)

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; CI = confidence interval; DM = diabetes mellitus; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; HTN = hypertension; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; SD = standard deviation

Other vitamins. We identified 12 eligible cohort studies that examined risk of AD in association with use of antioxidant and multivitamins.[60-71] These studies are summarized in Table 5; detailed evidence tables are provided in Appendix B. Eight studies used samples from U.S. communities,[62,64-66,68-71]one used a sample from a medical cooperative organization in the United States;[63] two from communities in Europe,[60,61] and one from Canada.[67] Length of followup across the studies ranged from approximately 2 to 33 years. In all studies, participants were non-demented at baseline. Studies using food intake of E and C vitamins, beta carotene, or flavonoids as the predictor variables estimated intake from self-reported responses on nutrition questionnaires. Studies using intake of E and C vitamin supplements as the predictor variables estimated intake from self-reported use; some studies confirmed use of supplements by examination of medication containers. One study used medical records to obtain information on use of supplements for institutionalized participants.[67] Two studies reported on the same cohort, the Honolulu-Asia Aging Study,[64,66] but appeared to use different sources for their exposure data. Another two studies reported on the same sample but defined the predictor variable somewhat differently.[69,70] Yet another study used two distinctly different food frequency questionnaires for different subgroups of the sample and then developed a method to combine the information from both questionnaires into a single dataset.[61] In general, little validation has been done on the accuracy of the nutrition questionnaires in these studies, but one research group that reported on two different samples[68-70] has published some analyses showing that the food frequency questionnaires used in their studies were reasonably reliable and valid,[59] and that the performance characteristics did not vary significantly by cognitive ability. Correlations between responses on a food frequency questionnaire and a 24-hour dietary recall typically ranged from 0.39 to 0.67 for vitamins C and E, and were higher when vitamin supplements were considered.[59] Eleven of the studies used sample selection methods to minimize selection bias. One study[67] used a subsample from a larger cohort study, of which a disproportionate segment of the sample was at relatively high risk of cognitive impairment; part of this study sample was drawn from institutionalized participants and part from community participants. The sources of exposure information differed for these two subgroups, introducing additional potential sources of bias. Eight studies compared some baseline characteristics by exposure level.[60,63,65,67-71] All studies used standard criteria for the diagnosis of AD, but only five used an informant report as part of the diagnostic process.[60,62,64,66,71] All but one study[61] reported results for AD cases only, but the study that reported results for dementia as a whole included enough AD cases to meet our eligibility criteria. Few of the studies explicitly stated that the dementia diagnosis was assigned blind to the exposure level of the nutrients of interest; however, it is unlikely that details of these types of exposure were discussed during the diagnostic process in any of the studies. Analyses were appropriate and generally controlled for relevant potential confounders.

Results from the studies combined are inconclusive. The preponderance of evidence suggests that there is no association between the amount taken in of vitamins E or C, flavonoids, or beta carotene and risk of AD. However, selected studies have reported associations between AD and vitamin C,[60,68] vitamin E,[64,69] or the combination of the two vitamins.[71] When significant associations were reported, higher intake of the vitamin was associated with lower risk of AD (see Table 5). However, within studies these findings were often not consistent. For example, sometimes the significant association was limited to food intake only and not supplemental vitamins,[69] and in other studies the association between vitamin intake and AD was limited to alternating quintiles of vitamin level.[64] This raises some questions about the robustness of the

findings and leads to the conclusion that there is little evidence supporting a beneficial effect of antioxidant vitamins on reducing risk of AD.

Table 5. Antioxidant and multivitamin use and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Engelhart et al., 2002[60]	Community cohort (5395)	6 years 146 AD cases	Dietary intake assessed with 2-stage protocol. First, self-report checklist of foods and drinks consumed at least twice a month during the preceding year. The checklist included questions on dietary habits, use of supplements, and prescribed diets. Based on checklist responses, participant interviewed by dietitian, using an extensive, validated semi-quantitative food-frequency questionnaire (SFFQ). Estimated intake of vitamins C and E, beta carotene, and flavonoids from SFFQ.	NINCDS-ADRDA DSM	Age Sex Educational level Baseline cognitive status Alcohol use Smoking BMI Total energy intake Presence of carotid plaques Supplemental antioxidant use	Adjusted HR (95% CI) for risk of AD for every SD increase in dietary intake: Vitamin C: HR 0.82; 0.68 to 0.99 Vitamin E: HR 0.82; 0.66 to 1.00 Beta carotene: HR 0.87; 0.70 to 1.09 Flavonoids: HR 0.99; 0.83 to 1.18
Fillenbaum et al., 2005[62]	Community cohort (616)	3 to 10 years 93 AD cases	Information obtained on supplemental use of C, E and multi-vitamins in previous 2 weeks based on review of medication bottles. Use of C or E in multivitamin categorized as low dose, and C or E not as part of a multivitamin as high dose	NINCDS-ADRDA DSM	Age Educational level Marital status Income Functional status Health services use Number of prescription drugs Time frame of exposure to vitamins	Vitamin E and/or C use at baseline or at wave prior to dementia diagnosis was not associated with incident AD.
Gray et al., 2008[63]	Clinical cohort – Group Health Co-operative (2969)	Mean 5.5 (SD, 2.7) years 289 AD cases	Self-report at baseline and each biennial followup interview whether they had taken vitamin C,vitamin E, or multivitamins for at least 1 week during the previous month. Categorized as vitamin E user if reported taking vitamin E supplements	NINCDS-ADRDA DSM	Age Sex Educational level Exercise Smoking status Self-reported health	Adjusted HR (95% CI) for possible or probable AD: No vitamins (n = 106): 1.0 (referent) Any vitamin E (n = 89): 1.04 (0.78 to 1.39) Any vitamin C (n = 105): 0.95

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
			(excluding multivitamins). Categorized as vitamin C users if they reported taking vitamin C supplements (excluding multivitamins).		Coronary heart disease	(0.72 to 1.25) Any multivitamin (n = 134): 0.94 (0.72 to 1.22) Combining vitamins did not change results.
Com-menges et al., 2000[61]	Community cohort (1367 analytical sample)	2 to 5 years 66 dementia cases, of which 46 were AD cases	At one study site, the participant was given a detailed questionnaire on which to record all food consumption over 3 days. Three days later, a dietitian conducted a historical inquiry about food consumption to assess frequencies and then completed the quantitative questionnaire. At the other site, a coarse questionnaire inquiring about intake of 20 categories of foods was administered. Frequency of consumption was assessed qualitatively. A self-reported quantitative interview of wine consumption was administered to all participants. The authors developed a method to combine the data from the two sources and estimate percent of flavonoid intake	DSM	Age Sex Educational level Weight Vitamin C	Flavonoid values in the upper 2 tertile levels combined were associated with lower rate of dementia compared to the lowest tertile (adjusted HR 0.49; 95% CI 0.26 to 0.92). If the upper 2 tertiles were not combined, only the middle tertile showed a protective association between flavonoid values and dementia (adjusted HR 0.45; 0.22 to 0.92). Wine intake was not associated with lower risk of dementia.
Laurin et al., 2004[64]	Community cohort (2459)	Range: 25.7 to 33.0 years 102 cases AD	Vitamin C, E, and beta carotene intake was extracted from self-reported 24-hour dietary recall during 1965–1968. Dietitians trained in standardized procedures used appropriate food models and serving utensils to establish food consumption. Participants were asked whether the 24-hour recall was fairly typical or unusual. In addition, questions	NINCDS-ADRDA DSM	Age Educational level Smoking Alcohol use BMI Physical activity Blood pressure Year of birth Total energy intake	Beta-carotene: No difference in risk of AD and mixed AD/vascular associated with higher quartiles of intake Vitamin C: No difference in risk of AD and mixed AD/vascular associated with higher quartiles of intake Vitamin E: 2nd and 4th quartiles only associated with higher risk of AD and mixed AD/vasc (but not

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
			related to the frequencies of consumption of 26 selected food and drink items characteristic of Western or traditional Japanese diets, including tea, were asked in 1965 to 1968 and 1971 to 1974.		Cholesterol History of cardiovascular disease APOE Supplemental vitamins	the 3rd quartile) 2nd quartile: HR 1.92 (1.16 to 3.18) 3rd quartile: HR 1.35 (0.78 to 2.31) 4th quartile: HR 1.78 (1.06 to 2.98) Flavonoids: No difference in risk of AD associated with higher quartiles of intake No significant trends across quartiles noted for any of the anti-oxidants Highest group of sum of all antioxidant intake associated with increased risk of AD and AD mixed/vascular dementia compared to lowest summed group (HR 1.82; 1.04 to 3.21) Authors concluded that midlife dietary intake of antioxidants does not alter risk of AD.
Luchsinger et al., 2003[65]	Community cohort (980)	4 (SD 1.5) years 242 AD cases	Daily dietary, supplement and total intake of carotenes, and vitamins C and E estimated from self-reported responses on semi-quantitative food frequency questionnaire	NINCDS-ADRDA DSM	Age Sex Educational level APOE Smoking	Compared to lowest intake quartile, dietary intake (excluding supplements) of: Carotenoids showed no association with AD at the higher intake quartiles Vitamin C showed no association with AD at the higher intake quartiles Vitamin E showed no association with AD at the higher intake quartiles Compared to lowest intake quartile, combined supplemental and dietary intake of: Vitamin C showed no association with AD at the higher intake

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
						quartiles Vitamin E showed no association with AD at the higher intake quartiles
Masaki et al., 2000[66]	Community cohort (but also some nursing home residents) (3385)	3 to 5 years for main analyses (subgroup of long term users 11 to 13 years) 47 AD cases	Self-reported responses to a mailed survey asking whether they had taken multivitamins or additional vitamin A, C, or E pills in the prior year. Details on number of pills taken each week were collected. Categorized as C and E supplement users when the number of pills taken each week was greater than zero.	NINCDS-ADRDA DSM	Age Educational level Childhood years spent in Japan APOE History of stroke	Compared to individuals who did not take either vitamin C or E, risk of AD was not reduced for those who took vitamin C without vitamin E (OR 1.61; 95% CI 0.67 to 3.87), nor for those who took vitamin E without C (OR 0.84; 0.19 to 3.77), nor vitamins E and C (OR 1.81; 0.91 to 3.62).
Maxwell et al., 2005[67]	Community cohort (but also some nursing home residents) (894)	Approxi-mately 5 years 107 AD cases	For non-institutionalized individuals, self-reported information on supplemental vitamin E and C use. Sometimes confirmed by review of medication bottle. For institutionalized individuals, information on supplemental vitamin E and C use from medical record.	NINCDS-ADRDA DSM	Age Sex Educational level Blood pressure Baseline cognitive status Institutional residence	Combined use of vitamins E and C was not associated with risk of AD (adjusted OR 1.00; 95% CI, 0.53 to1.87). Use of vitamin E or C not associated with risk of AD
Morris et al., 1998[68]	Community cohort (633)	4.3 years 91 AD cases	Supplemental vitamin E and C use from self-reported information on medications taken in the previous 2 weeks. Confirmed by visual examination of medication bottles.	NINCDS-ADRDA	Age Sex Educational level Time to followup Sample weight	Fewer than expected incident AD cases used vitamin C (p = 0.04) No difference in expected AD incidence and observed incidence among vitamin E users (p = 0.23)
Morris et al., 2002[69]	Community cohort (815)	3.9 years 131 AD cases	Estimates of total intake of vitamins E and C during the previous year were calculated from self-report responses on a modified Harvard food frequency questionnaire	NINCDS-ADRDA	Age Race Sex Educational level APOE	For vitamin E from food intake only (not food and supplement), the highest quintile of vitamin E intake was associated with lower risk of AD (RR 0.30; 95% CI 0.10 to 0.92); trend for all quintiles p = 0.05.

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
					Time interval to followup	Vitamin E intake from food and supplements was not associated with risk of AD. Vitamin C from intake from food only was overall not significantly associated with AD. P value for trend did not approach significance. Quintile 4 only was associated with reduced risk of AD (RR 0.37; 0.17 to 0.82) Vitamin C intake from food and supplements was not associated with risk of AD. For beta-carotene, neither intake of food only or food plus supplements was associated with risk of AD. Among APOE e4 negatives, vitamin E intake from food was associated with reduced incidence of AD among quintiles 3, 4, and 5 (quintile 5 RR 0.17; 95% CI 0.06 to 0.47). In APOE e4 positives, vitamin E was not protective against AD.
Morris et al., 2005[70]	Community cohort (1041)	2.7 years 162 AD cases	Estimates of total food intake for all eight forms of vitamin E from food during the previous year were calculated from self-report responses on a modified Harvard food frequency questionnaire	NINCDS-ADRDA	Age Race Sex Educational level APOE Cognitive activities Observation interval Saturated fat Trans unsaturated fat DHA Vitamin C	Lower AD risk associated with high intake of: Vitamin E: RR 0.74; 95% CI 0.62 to 0.88 Gamma-tocopherol: RR 0.60; 0.41 to 0.88) Delta-tocopherol: RR 0.75; 0.58 to 0.96) Alpha-tocopherol equivalents: (RR 0.56; 0.32 to 0.98)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Zandi et al., 2004[71]	Community cohort (3227)	3 years 104 AD cases	Self-reported use of supplemental vitamin E and C during the preceding 2 weeks. Confirmed by review of medication containers. Vitamin E users defined as those taking a multivitamin or vitamin E supplemental containing more than 400 IU. Vitamin C users defined as taking vitamin C supplements or multivitamin preparations containing at least 500 mg of ascorbic acid. Multivitamin users defined as use of a multivitamin preparation containing lower doses of vitamin E or C.	NINCDS-ADRDA DSM	Age Sex Educational level APOE General health status	Reduced risk of incident AD associated with combined vitamin E and C use (HR 0.36; 95% CI 0.09 to 0.99) No significant association between incident AD and vitamin E alone, vitamin C alone, multivitamin, or B-complex vitamins, or any combination of these except for vitamins E and C combined.

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; APOE e4 = e4 allele of the apolipoprotein E gene; BMI = body mass index; CI = confidence interval; DHA = docosahexaenoic acid; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; RR = relative risk; SD = standard deviation

Gingko biloba. We did not identify any eligible studies examining risk of AD in relation to use of gingko biloba supplements.

Omega-3 fatty acids. We identified two good quality systematic reviews evaluating the association between omega-3 fatty acids and risk of Alzheimer's disease.[29,30] We focus the discussion on the more recent (2009) review by Fotuhi et al.[29] The review included seven prospective cohort studies described in nine publications dating from 1997 to 2008.[60,72-79] The seven studies included a total of 18,922 subjects; three were conducted in the United States, three in European countries, and one in Canada (Table 6). Prospective observational studies or trials were selected that addressed the specific association between any form of omega-3 fatty acids and dementia in participants age 65 or older, and that used standard diagnosis of dementia. The number of individuals with AD versus other dementias was available, and all studies met our eligibility threshold of at least 60 percent with AD. There was not a structured quality assessment of studies reported in this systematic review; however study characteristics for key design variables were reported, and study selection criteria focused the review on higher quality studies. Length of followup ranged from 3.9 to 7 years. No information was given on followup rates. Covariate adjustment included age, sex, and education, and many studies included additional covariates such as the apolipoprotein E gene (APOE), other nutritional factors, and income. Covariate adjustment for education and income may be particularly important as several studies reported an association between fish consumption and higher incomes and education. Both unadjusted and adjusted results were reported. Omega-3 fatty acid intake was estimated by dietary histories in six studies; one[74] measured serum polyunsaturated fatty acids (PUFAs) and one reported plasma PUFAs in a subsample.[79] Most studies focused on fish consumption to estimate omega-3 fatty acids without considering other dietary sources or fish oil supplements. Exposure classification varied substantially ranging from a simple count of the frequency of fish servings per week to estimates of the number of grams consumed per day. Because of significant study heterogeneity in study design, results were synthesized qualitatively.

Study characteristics and results are summarized in Table 6. There was no consistent association between omega-3 fatty acid intake and incident AD. Three of the seven cohort studies showed that fish consumption was associated with a statistically significant reduced risk of AD;[73,75,78] three did not show a statistically significant association,[72,76,77] although the point estimate favored a lower risk in two studies; and one small study[74] showed higher serum PUFAs in subjects who developed dementia. Two studies examined the interaction between fish intake and APOE, one showing no interaction,[78] and one showing an interaction where increased fish consumption decreased risk of AD only in those who were non-carriers of the epsilon 4 allele of the apolipoprotein E gene (APOE-e4).[76] There was substantial heterogeneity in how omega-3 consumption was assessed, including differences in the types of fish (e.g., fatty versus non-fatty), dosage, and duration of use. Most studies focused only on long-chain omega-3 fatty acids and not on specific fatty acids (e.g., docosahexaenoic acid [DHA]) or the ratio of omega-3 to omega-6 fatty acids, a ratio that has been linked to some cardiovascular outcomes. The variability in exposure intake may be an important contributor to inconsistent study findings. The authors concluded that the existing data do not favor a role for long-chain omega-3 fatty acids in preventing dementia, including AD.

Table 6. Omega-3 fatty acids and risk of developing AD – study characteristics and results from studies reviewed by Fotuhi et al., 2009[29]

Study	Sample size (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Kalmijn et al., 1997[72] and Englehart et al., 2002[60]	Community cohort (5386)	2.1 years 58 dementia (42 AD)	Fat intake by history at baseline (n-3 PUFAs estimated by fish intake; n-6 PUFA estimated by linoleic acid intake)	DSM NINCDS-ADRDA 72% of dementia cases classified as AD	Age Sex Education Total energy intake	Higher fish intake associated with lower risk of dementia (> 18.5 g/day: RR 0.4; 95% CI 0.2 to 0.9; 3 to 18.5 g/day: RR 0.8; 95% CI 0.4 to 1.4 compared to ≤ 3.0 g/day). Higher linoleic acid intake not associated with dementia risk (> 15.0 g/day: RR 0.6; 95% CI 0.3 to 1.2), 9.5 to 15.0 g/day: RR 1.2; 95% CI 0.7 to 2.3) compared to ≤ 9.5 g/day.
Barberger-Gateau et al., 2002[73]	Community cohort (1416)	7 years 170 (130 AD)	Fish intake by dietary history	DSM	Age Sex Education	RR for AD 0.69 (95% CI 0.47 to 1.01)
Laurin et al., 2003[74]	Community cohort (79)	5 years 11 dementia	Total serum PUFAs and omega-3 PUFAs	DSM NINCDS-ADRDA	Age Sex Education APOE Smoking Alcohol use Cardiovascular disease BMI	Participants who developed dementia had higher concentrations of omega-3 PUFAs by 21% (p = 0.04) and total PUFAs by 6% (p = 0.03)
Morris et al., 2003[75]	Community cohort (815)	3.9 years 131 AD	Fish, total n-3 fatty acids, EPA, linolenic acid by dietary history	NINCDS-ADRDA	Age Race Sex Education APOE Time to followup	Higher fish intake decreased risk of AD: ≥ 2 times weekly: RR 0.4; 95% CI 0.2 to 0.9 Once weekly: RR 0.4, 0.2 to 0.9 1 to 3 times monthly: 0.6, 0.3 to 1.3 compared to never Higher total n-3 fatty acids and

Study	Sample size (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
						higher DHA but not EPA or linolenic acid associated with decreased risk of AD
Huang et al., 2005[76]	Community cohort (2233)	9 years 190 AD	Fried fish and Fatty fish intake by dietary history (servings/week)	NINCDS-ADRDA	Age Race Sex Education Income APOE Total energy intake BMI Study site	Fried fish not associated with AD: 0.25 to 2 servings/week: HR 0.97 (95% CI 0.67 to 1.4) ≥ 2 servings/week: HR 0.95 (0.60 to 1.52) Tuna or other fish not associated with AD: 0.25 to 2 servings/week: HR 0.85 (0.54 to 1.33) 2-4 servings/week: HR 0.72 (0.44 to 1.17), > 4 servings/week: HR 0.69 (0.91 to1.22)
Schaefer et al., 2006[77]	Community cohort (899)	9.1 years 99 dementia (71 AD)	DHA by dietary history and plasma levels (quartiles); fish intake by dietary history	DSM NINCDS-ADRDA	Age Sex Education APOE Homocysteine	Highest quartile for plasma DHA levels (RR 0.61; 95% CI 0.31 to 1.18), dietary intake of DHA (RR 0.62, 0.23 to 1.72) and fish > twice weekly (RR 0.61, 0.28 to 1.33) compared to lower 3 quartiles was not associated with reduced risk of AD.
Barberger-Gateau, et al., 2007[78] and Samieri et al., 2008[79]	Community cohort (8085; 1214 in substudy)	3.48 years 281 dementia (183 AD)	Fish and other dietary sources of omega-3 by dietary history; Plasma PUFAs in subsample	DSM NINCDS-ADRDA	Age Sex APOE e4 Education Income Marital status BMI Diabetes	Fish once weekly: HR 0.74 (95% CI 0.46 to 1.17) 2-3 times weekly: HR 0.59 (0.37 to 0.94) ≥ 4 times weekly: HR 0.58 (0.25 to 1.34) Plasma EPA concentration inversely association with incident dementia

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; APOE e4 = e4 allele of the apolipoprotein E gene; BMI = body mass index; CI = confidence interval; DHA = docosahexaenoic acid; DSM = Diagnostic and Statistical Manual of Mental Disorders; EPA = eicosapentaenoic acid; HR = hazard ratio; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; PUFA(s) = polyunsaturated fatty acid(s); RR = relative risk; SD = standard deviation

We identified two additional eligible studies published after the above-described review appeared (Table 7). Devore and colleagues[80] prospectively followed 5396 subjects from Rotterdam for a mean of 9.6 years. Fish and other dietary sources of omega-3 were assessed at baseline using a dietary history. Kroger and colleagues[81] used a nested case-control design to evaluate the association between blood and erythrocyte membrane PUFAs and AD in a community sample from Canada. This represents an updated analysis of the study by Laurin et al.,[74] which was included in the 2009 systematic review described above.[29] Only 15 percent of the overall sample provided blood samples, potentially introducing selection bias. Both studies established AD using the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and controlled for multiple potential confounders including age, educational level, and vascular risk factors. Neither study found an association between fish intake, total PUFAs, DHA, or eicosapentaenoic acid (EPA).

In summary, a previous systematic review of seven prospective studies concluded that there was no consistent association between PUFAs, usually estimate by dietary histories of fish consumption, and incident AD. Results from a relatively large observational study with longer-term followup published since the 2009 systematic review, and from a reanalysis of a previously published study, are consistent with this conclusion.

Table 7. Omega-3 fatty acids and risk of developing AD – recent cohort studies

Study	Sample size (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Devore et al., 2009[80]	Community cohort (5395)	Mean 9.6 years 365 AD of total 465 incident dementia	Total and fatty fish intake at baseline PUFAs at baseline by food frequency questionnaire	NINCDS-ADRDA	Age Sex Education Total energy intake Alcohol BMI Total cholesterol Dietary vitamin E Supplement use Vascular risk factors	AD risk for high vs. no fish intake: HR 0.99 (95% CI 0.76 to 1.29) No association for long chain omega-3, EPA, or DHA intake
Kroger et al., 2009[81]	Community cohort (663)	Median 4.9 years 105 AD of total 149 incident dementia	Blood total and erythrocyte membrane PUFAs at baseline	NINCDS-ADRDA	Age Sex Education Alcohol BMI Vascular risk factors History of depression Family history of dementia	No association for dementia or AD with total PUFA, EPA, or DHA AD risk for highest quartile of total PUFA: HR 1.12 (95% CI 0.63 to 1.98)

Abbreviations: AD = Alzheimer's disease; BMI = body mass index; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HR = hazard ratio; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; PUFA(s) = polyunsaturated fatty acid(s); RR = relative risk

Other fats. We identified two eligible cohort studies examining risk of AD in relation to intake of various types of fat.[82,83] These studies are summarized in Table 8; detailed evidence tables are provided in Appendix B. One study used a community sample in the United States,[82] and the other used a community sample in Europe.[83] Length of followup ranged from 3.9 to 21 years. In one study, [82] exposure was determined based on self-reported information from a semi-quantitative food frequency questionnaire in late-life. Based on a validation substudy, the authors reported the Pearson correlations for comparative validity with 24-hour dietary recalls were 0.40 for monounsaturated fat, 0.47 for saturated fat, 0.36 for polyunsaturated fat, and 0.39 for cholesterol. In the other study,[83] exposure was determined based on a self-reported, 20-question, multiple-choice questionnaire completed in mid-life.[83] This study estimated the total fat intake from milk products and dairy product spreads based on questionnaire responses. Both studies used sample selection methods to minimize selection bias, but only one compared baseline characteristics by exposure level.[82] Investigators used standard criteria for the diagnosis of AD, but they did not use an informant report as part of the diagnostic process. One study stated that dementia diagnosis was assigned blind to the exposure level;[82] it is assumed here that this was also the case in the other study.[83] Analyses were appropriate and controlled for relevant potential confounders in one study,[82] and partially controlled for potential confounders in the other study.[83]

The study assessing mid-life dietary fat intake[83] did not find a significant association between risk of AD and intake of total fat, polyunsaturated fats, or monounsaturated fats. Investigators did report significant increased risk of AD associated with the 2nd quartile of saturated fat intake compared with the 1st quartile; however, this increased risk did not hold up across the top two quartiles, raising questions about the robustness of the result. The study assessing later life dietary fat intake[82] reported increased risk of AD associated with increased intake of saturated fats and trans-unsaturated fats, and a decreased risk of incident AD associated with higher intake of w-6 polyunsaturated fats. Differences between the studies in how the level of exposure was determined and the time when the exposure occurred may explain the discrepant results, but such fundamental differences also make it difficult to draw conclusions from these two studies. The study by Morris and colleagues[82] used the most detailed dietary intake data. Giving weight to this study based on the data quality, there are preliminary data that saturated fats and trans-unsaturated fats may contribute to an increased risk of AD. Confirmation of these findings is needed.

Table 8. Intake of various types of fat and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Morris et al., 2003[82]	Community cohort (815)	Mean 3.9 years 131 AD cases	Self-reported responses on a revised Harvard self administered food-frequency questionnaire	NINCDS-ADRDA	Age Race Sex Educational level APOE	Saturated fat: Highest quintile associated with increased risk of AD: RR 2.2 (95% CI 1.1 to 4.7) Trans-unsaturated fat: Quintiles 2 to 5 higher risk of AD, but only quintiles 2 (2.4 ;1.1 to 5.3) and 3 (2.9; 1.2 to 7.2) significant w-6 polyunsaturated fat: Quintile 5 had lower risk of AD (0.3; 0.1 to 0.8) Monounsaturated fat, total fat and dietary cholesterol not associated with AD Animal fat and vegetable fat not associated with AD in multivariable models, but when vegetable fat controlled for other dietary fat, there was a linear trend (p = 0.002) for protection against AD (although the RR for individual quintiles was not significant). The p value for trend was not significant for any other type of fat.
Laitinen et al., 2006[83]	Community cohort (1449)	Mean 21 years 48 AD cases	Self-reported responses on 20 multiple choice questions about dietary habits	NINCDS-ADRDA DSM	Age (midlife) Sex Educational level Followup time Milk fat and other types of fats from spreads Midlife vascular risk factors APOE History of vascular disorders collected at followup	Total fat: 2nd, 3rd and 4th quartiles of total fat intake was not associated with increased risk of AD (compared to 1st quartile) PUFA: 2nd, 3rd and 4th quartiles of PUFA intake from spreads not associated with lower risk of AD in fully adjusted models (compared to 1st quartile) MUFA: 2nd, 3rd and 4th quartiles of MUFA intake from spreads was not associated with increased risk of AD (compared to 1st quartile) SFA: 2nd quartile of SFA intake from spreads was associated with increased risk of AD(compared to 1st quartile) OR 3.82 (95% CI 1.48 to 9.87), but 3rd and 4th quartiles not associated with increased risk

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; CI = confidence interval; MUFA = monounsaturated fatty acid; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; PUFA = polyunsaturated fatty acid; RR = relative risk; SFA = saturated fatty acid

Trace metals. We identified no systematic reviews or studies evaluating a potential association between trace metals and reduction of risk of Alzheimer's disease.

Mediterranean diet. We identified four eligible cohort studies examining risk of AD and the Mediterranean diet.[84-87] The Mediterranean diet is characterized by high intake of vegetables, legumes, fruits, and cereals; high intake of unsaturated fatty acids (mostly in the form of olive oil), but low intake of saturated fatty acids; a moderately high intake of fish; a low-to-moderate intake of dairy products (mostly cheese or yogurt); a low intake of meat and poultry; and a regular but moderate amount of alcohol, primarily in the form of wine and generally during meals. The included studies are summarized in Table 9; detailed evidence tables are provided in Appendix B. One study[87] used a community sample in Europe. The three other studies[84-86] were based on the same community sample in the United States, but they address slightly different outcomes or exposures. One study assessed the association between AD and the Mediterranean diet,[84] one assessed the association between progression from MCI to AD and the Mediterranean diet,[86] and one assessed the association between AD and the Mediterranean diet and physical activity combined.[85] For all of the studies, participants were non-demented at baseline, but for one[86] some of the participants were retrospectively assigned a diagnosis of MCI at baseline. Length of followup ranged from an average of 4 to 7 years. Exposure was determined based on self-reported information from a semi-quantitative food frequency questionnaire. Both studies used similar methods to calculate a Mediterranean diet score based on the responses on this questionnaire. Investigators in all studies noted that they had previously reported that this questionnaire has adequate validity and reliability based on substudies of segments of the questionnaire. All of the studies used sample selection methods to minimize selection bias and compared baseline characteristics by exposure level. Investigators used standard criteria for the diagnosis of AD, but did not use an informant report as part of the diagnostic process. One study applied diagnostic criteria for MCI retrospectively.[86] It is assumed here that the dementia and MCI diagnoses were assigned blind to the exposure level, but this information was not provided in some of the publications. Analyses were appropriate and controlled for relevant potential confounders.

The three publications based on the single cohort[84-86] reported fairly consistent results regarding the association between higher compliance with a Mediterranean diet and a significantly lower risk of incident AD. The studies reported significant trend effects, suggesting a dose-response pattern. The study on this cohort examining the progression of MCI to dementia found that higher adherence to a Mediterranean diet was associated with a lower risk of progressing from MCI to AD.[86] Another study on this cohort examined the combination of physical activity and diet; the authors reported that a lower risk of AD was associated with those who both highly adhered to a Mediterranean diet and participated in much physical activity. Low adherence to a Mediterranean diet combined with high levels of physical activity, or vice versa, did not provide a protective association for AD. The one study on a separate sample[87] reported a hazard ratio in the direction indicating that high adherence to a Mediterranean diet was associated with lower risk of AD, but the hazard ratio did not meet standard significance levels. The authors of this manuscript noted that the sample had limited power to detect an association, and this may explain their null finding.

In conclusion, multiple studies on one cohort reported that high adherence to a Mediterranean diet is associated with lower risk of AD; one study on a separate sample did not replicate this finding, but this may be due to lack of statistical power. Confirmation of the reported protective association of a Mediterranean diet is needed using an independent sample.

Table 9. Mediterranean diet and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Scarmeas et al., 2006[84]	Community cohort (2258)	Mean 4.0 (3.0) years 262 AD cases	Self-reported responses on a food frequency questionnaire	NINCDS-ADRDA DSM	Age Race Sex Educational level Sample cohort APOE Caloric intake Smoking Medical comorbidity index BMI	Higher adherence to a Mediterranean diet was associated with decrease in risk of AD: Continuous measure of Mediterranean diet: HR 0.91 (95% CI 0.83 to 0.98) Categorical measure: High tertile (HR 0.60; 0.42 to 0.87) p = 0.007 for trend
Scarmeas, et al., 2009[85]	Community cohort (1880)	Mean 5.4 (3.3) years 282 AD cases	Self-reported responses on a food frequency questionnaire and self-reported responses on a leisure time exercise questionnaire	NINCDS-ADRDA DSM	Race Sex Educational level BMI Smoking Depression Leisure activities Comorbid medical conditions Baseline CDR score APOE Interval between 1st dietary and 1st physical activity measure Caloric intake	Higher adherence to both a Mediterranean diet and physical exercise associated with decrease in risk of AD: Considered simultaneously, high diet score (compared to low diet score): HR 0.60 (95% CI, 0.42 to 0.87) And much physical activity (compared with no physical activity): HR 0.67 (95% CI, 0.47 to 0.95) Absolute risk for AD 19% for individuals with both low diet score and no physical activity, compared to absolute risk for AD of 12% for individuals with high diet score and high physical activity: HR 0.65 (95% CI, 0.44 to 0.96)
Scarmeas, et al., 2009[86]	Community cohort (1875)	Mean 4.5 (2.7) years 275 incident MCI cases 107 incident	Self-reported responses on a food frequency questionnaire	NINCDS-ADRDA DSM MCI criteria applied currently accepted diagnostic criteria to previously collected data	Age Race Sex Education APOE BMI	Compared to lowest tertile diet score, HR for progression from MCI to AD for middle tertile diet score = 0.55 (95% CI 0.34 to 0.90) and highest tertile diet score = 0.52 (95% CI 0.30 to 0.91)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
		AD cases			Interval between dietary assessment and cognitive assessment	
Feart et al. 2009[87]	Community cohort (1410)	7 years 66 AD cases	Self-reported responses on a food frequency questionnaire	DSM	Age Sex Education Marital Status Energy Intake Physical Activity Depressive symptomatology Taking 5 medications or more APOE Cardiovascular risk factors Stroke	High Mediterranean diet score (6 to 9), HR 0.86 (95% CI 0.39 to 1.88), and middle scores (4 to 5), HR 0.99 (0.51 to1.94), compared to low scores (0 to 3) were not associated with lower rates of AD

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; BMI = body mass index; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association

Fruit and vegetable intake. We identified two eligible cohort studies examining risk of AD in relation to intake of fruit and vegetables[88]or intake of fruit and vegetable juices containing a high concentration of polyphenols.[89] These studies are summarized in Table 10; detailed evidence tables are provided in Appendix B. One study[89] used a community sample in the United States, and the other used a twin registry in Europe.[88] Length of followup ranged from an average of 6.3 to 31.5 years. In one study,[88] exposure was determined based on self-reported responses to one question on fruit and vegetable consumption; in the other study,[89] exposure was determined by self-reported information from a semi-quantitative food frequency questionnaire. The investigators conducted a validation study of the questionnaire and found low to moderate correlations (0.42 to 0.77) between food records and responses on the food frequency questionnaire for major nutrient groups for the ethnic groups included in the study. Both studies used sample selection methods to minimize selection bias, and one[89] compared baseline characteristics by exposure level. Investigators used standard criteria for the diagnosis of AD, but only one of the studies[89] used an informant report as part of the diagnostic process. Only one study[88] reported that the dementia diagnosis was assigned blind to the exposure level, but since this type of exposure is not typically discussed as part of the dementia assessment and diagnosis process, it is assumed here that the diagnosis was assigned blind to exposure in both studies. Analyses were appropriate and controlled for relevant potential confounders.

One of the studies reported that medium to great fruit and vegetable intake in mid-life was associated in lower risk of AD in late life.[88] This association was present in women, but not in men. It was also present in individuals with angina, but not in those without angina. This study used a crude measure (one self-report question) to determine exposure. The other study showed that intake of fruit or vegetable juice at least three times per week in later life, compared to less than once per week, was associated with reduced risk of incident AD.[89] A significant trend was noted, suggesting a dose-response pattern.

In conclusion, these two studies offer preliminary evidence that higher intake of fruit and vegetable juices throughout adult life may provide benefits for preventing AD, but the findings need to be confirmed.

Table 10. Intake of fruit and vegetables and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Dai et al., 2006[89]	Community cohort (1589)	Mean 6.3 years (SD 2.6) 63 AD cases	Fruit and vegetable juice intake estimated from self-reported, self-administered semi-quantitative food frequency questionnaire	NINCDS-ADRDA DSM	Age Sex Educational level Baseline cognitive status Physical activity BMI Olfaction diagnostic group Total energy intake Intake of types of fat APOE Smoking Alcohol use Vitamin C, E, and multivitamin supplement use	Individuals who had fruit and vegetable juice at least once a week were less likely to get AD (trend $p < 0.01$) HR for 1 to 2/week: 0.84 (95% CI 0.31 to 2.29) HR for ≥ 3/week: 0.24 (0.09 to 0.61)
Hughes et al., 2009[88]	Other – Twin Registry cohort (3779)	Mean 31.5 years (SD 0.91)	Self report response on one question about fruit and vegetable consumption	NINCDS-ADRDA DSM	Age Sex Educational level Smoking Alcohol use Exercise BMI Angina Marital status Total food intake	Medium or great fruit and vegetable intake in mid-life associated with lower risk of AD (OR 0.60; 95% CI 0.41 to0.86) Medium or great fruit and vegetable intake in mid-life associated with lower risk of AD in women (OR 0.47; 0.31 to 0.73) but not men. Interaction OR 0.45 (0.21 to 0.98). Medium or great fruit and vegetable intake in mid-life associated with lower risk of AD in those with angina (OR 0.32; 0.16 to 0.65), but not in those without angina. Interaction OR 0.44 (0.21 to 0.95).

Abbreviations: AD = Alzheimer's disease; APOE = Apolipoprotein E gene; BMI = body mass index; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; SD = standard deviation

Total intake of calories, carbohydrates, fats, and proteins. We identified one eligible cohort study examining risk of AD and total intake of calories, carbohydrates, fats, and protein.[90] This study is summarized in Table 11; a detailed evidence table is provided in Appendix B. The study used a community sample in the United States. Length of followup averaged 4 years. Participants were non-demented at baseline. Exposure was determined based on self-reported information from a semi-quantitative food frequency questionnaire. The validity of the questionnaire used in this study was assessed previously in a subsample of individuals using two 7-day food records as the criterion. The intra-class correlations for energy-adjusted nutrients were 0.30 for total calories, 0.28 for carbohydrates, 0.41 for fats, and 0.33 for protein, based on energy-adjusted nutrient intakes. The study used sample selection methods to minimize selection bias and it compared baseline characteristics by exposure level. Investigators used standard criteria for the diagnosis of AD, but did not use an informant report as part of the diagnostic process. It was not reported whether the dementia diagnosis was assigned blind to the exposure level, but it is unlikely that this type of information would have been discussed during the diagnostic process. Analyses were appropriate and controlled for relevant potential confounders.

This study reported that higher caloric intake was associated with higher risk of incident AD. There was no association between AD risk and intake amounts of carbohydrates, fats, or protein. In analyses stratified by APOE e4 allele status, both total calorie intake and fat intake were associated with high risk of AD.

In conclusion, the findings from this single study are somewhat difficult to interpret given the hazard ratio (HR) < 2, which may suggest that residual confounding explains the association and the relatively low correlations reported in the study's validation of the instrument used to collect exposure. In addition, these findings may be inconsistent with other studies reporting that weight loss may be an antecedent of AD. However, the findings do suggest that high caloric intake may be an aspect of diet that should be investigated further in regards to its association with risk of AD.

Table 11. Total intake of calories, carbohydrates, fats, and protein and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Luchsinger et al., 2002[90]	Community cohort (980)	Mean 4 (SD 1.5) years 242 AD cases	Self-reported responses on a food frequency questionnaire	NINCDS-ADRDA DSM	Age Race Sex Educational level APOE	Total daily calories: Quartile 4 associated with increased risk of AD (HR 1.48; 95% CI 1.00 to 2.19) Carbohydrates: No association with AD Fats: No association with AD Protein: No association with AD Only APOE e4 positive associated with risk of AD for: Total calories: Quartile 4 HR 2.27 (1.11 to 4.68); p value for trend = 0.07 Fats: Quartile 4 HR 2.31 (1.09 to 4.89); p value for trend = 0.02

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; APOE e4 = e 4 allele of the apolipoprotein E gene; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; SD = standard deviation

Medical Factors

Vascular factors. Factors considered under this heading include diabetes mellitus, metabolic syndrome, hypertension, hyperlipidemia, and homocysteine.

Diabetes mellitus. We identified two good quality systematic reviews that examined the association between diabetes mellitus and the development of AD.[41,42] The review by Biessels and colleagues[41] included 11 cohort studies (101,972 subjects); five were from the United States, four from Western Europe, one from Canada, and one from Japan. Publication dates ranged between 1989 and 2005. Studies were selected that were longitudinal, had subjects recruited at the population level, and where the incidence of dementia could be compared between subjects with and without diabetes mellitus. Studies that included people with cognitive impairments but not dementia were excluded, as were studies of the prevalence of diabetes in patients with dementia. Data were presented for the effect of diabetes on any dementia, vascular dementia, and Alzheimer's disease, but the focus here is on Alzheimer's disease.

The review authors reported that the quality for cohort designs was fair to good, with 9 of 11 studies receiving a score of at least 6 points out of 10 using a scale that judged population selection and recruitment, participation at followup, dementia assessment and diagnosis, and data analysis. Length of study followup ranged from 2.1 to 35 years, with the age of recruited subjects ranging from 45 to 84 years. Diagnosis of diabetes varied. Six studies relied on medical history or medication use and did not assess blood glucose concentration in all participants. The prevalence of diabetes ranged from 8.8 percent to 35 percent of the study population. Six studies also assessed diabetes only at baseline, making it likely that a number of subjects who developed incident diabetes were assigned to the non-diabetic group. Studies did not distinguish between type 1 and 2 diabetes, but since all participants were middle-aged or older adults and type 2 diabetes predominates in this age group, almost all were likely to have type 2 diabetes. Data for diabetes duration, hemoglobin A_{1c}, and microvascular complications were not regularly reported. Most studies used the Diagnostic and Statistical Manual of Mental Disorders (DSM) III or IV criteria for the diagnosis of dementia and NINCDS-ADRDA criteria for AD. Six studies relied on a consensus committee to establish a diagnosis of dementia.

Biessels et al. did not combine data because of variability of study design, and assessment of heterogeneity was not reported.[41] The possibility of publication bias was considered, but a funnel plot was not performed. Covariates commonly considered included age, sex, education, and, in some studies, baseline cognitive performance and cardiovascular risk factors. Nine of 10 studies reported that participants with diabetes had an increased risk of developing Alzheimer's disease, with relative risk, odds ratios, or hazard ratios greater than 1 (range 1.2 to 2.4), and with 95 percent confidence intervals > 1.0 in five studies. Adjustment for vascular risk factors was examined in five studies; four of the five reported a relative risk or hazard ratio greater than 1 (range in all studies 0.8 to 2.0), but for only two of these did the adjusted HR exclude no effect. Two studies examined the risk of developing Alzheimer's disease in individuals who had midlife assessment of diabetes status. Yamada et al.[91] reported an odds ratio (OR) of 4.4 ($p < 0.01$), and Curb et al.[92] reported a relative risk (RR) of 1.0 (95 percent confidence interval [CI] 0.5 to 2.0) for individuals with diabetes mellitus developing Alzheimer's disease.

Longitudinal studies in which diabetes and dementia were assessed in late life demonstrated fairly consistent results. Seven of 11 studies reported a 50 to 100 percent increase in the incidence of AD. Two studies examined the effect of APOE genotype and found that the presence of an e4 allele doubled the relative risk of dementia in diabetics compared to

participants with either of these risk factors alone. The authors concluded the literature suggests that the risk of AD is increased in patients with diabetes mellitus.[41]

A subsequent systematic review and meta-analysis by Lu and colleagues identified reports from two additional cohort studies examining the association between diabetes mellitus and the incidence of AD.[42] Akomolafe et al. reported results from 2210 participants in the Framingham study and found that diabetics had a non-statistically significant increase in risk compared to non-diabetics (RR 1.15; 95 percent CI 0.65 to 2.05).[93] Similar results were found in the Cache County Study of Memory, Health and Aging, where the RR for AD in diabetics was reported to be 1.33 (95 percent CI 0.66 to 2.46).[94] In their systematic review, Lu and colleagues,[42] in contrast to Biessels and colleagues,[41] judged that studies examining the effect of diabetes on dementia risk were sufficiently homogeneous, based on similar criteria for diagnosis and dementia, that meta-analysis was appropriate. They performed a meta-analysis on the adjusted relative risk of diabetics developing Alzheimer's disease using data from eight longitudinal, prospective cohort studies. The combined RR, using a fixed-effect model, was 1.39 (95 percent CI 1.17 to 1.66). A test for heterogeneity did not reveal significant heterogeneity between studies (χ-squared Q-test statistic 3.269, df = 5; p = 0.659), and visual inspection of funnel plots and Egger's test did not suggest publication bias. Lu and colleagues concluded, therefore, that diabetes mellitus was associated with an increased incidence of AD.[42]

We identified two additional studies on diabetes mellitus and the risk of developing AD that were published after the above-described systematic reviews (Table 12). Irie et al. examined the role of diabetes mellitus and APOE genotype on incidence of dementia in over 2000 participants in the Cardiovascular Health Study.[95] They found that diabetes or inheritance of APOE e4 alone each increased the risk of developing AD (OR 1.62; 95 percent CI 0.98 to 2.67; and OR 2.50; 95 percent CI 1.84 to 3.40, respectively) compared to individuals without diabetes or an APOE e4 allele. The OR for subjects with both diabetes mellitus and an APOE e4 allele was 4.99 (95 percent CI 2.70 to 9.20), which the author's suggested was evidence for an interaction between the risk factors. Xu et al. prospectively followed 1248 subjects from the Kungsholmen Project for an average of 5.1 years.[96] The average age of participants was approximately 82 years, and 75 percent were women. In a fully adjusted model the hazard ratio of incident AD for individuals with borderline diabetes was 1.87 (95 percent CI 1.11 to 3.14), and for undiagnosed diabetes the HR was 3.29 (95 percent CI 1.20 to 9.01), indicating an increased risk of AD. The risk for subjects with diagnosed diabetes was not statistically different from the risk for non-diabetics. No analysis of dementia risk as a function of hemoglobin A_{1c} level was reported. Xu and colleagues[96] suggested several possible explanations for their findings that borderline and undiagnosed diabetes place subjects at greater risk for AD than those with diagnosed diabetes: The number of subjects with diagnosed diabetes and dementia was relatively small, limiting the statistical power to identify a significant association; diabetics – because they were aware of their condition – may have altered their lifestyle, while subjects with borderline or undiagnosed diabetes would not be aware of their condition and, therefore, would not have modified their lifestyle; and the degree of hyperinsulinemia and insulin resistance might be different in borderline and undiagnosed diabetics than in known diabetics. Hyperinsulinemia and insulin resistance have been implicated in AD pathogenesis.

In summary, individual prospective, longitudinal cohort studies, two systematic reviews, and a meta-analysis all report an association between diabetes mellitus and incident Alzheimer's disease, but results in individual studies vary. Studies also suggest that inheriting an APOE e4 allele further increases the risk of AD in diabetics. Limitations of the included studies include

variable criteria for diagnosis of diabetes, failure to consider duration of diabetes, and degree of glycemic control. Additional research examining the age of diabetes onset (mid-life versus late-life onset), comorbid conditions (such as vascular risk factors), type of treatment (diet versus oral versus insulin), and the role of hyperinsulinemia on dementia risk is needed.

Table 12. Diabetes mellitus and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Irie et al., 2008[95]	Community cohort (2547 – 602 with APOE e4; 320 with DM) Random selection Medicare recipients aged > 65 in 4 counties	Mean 5.4 years; range up to 10 years	APOE genotype Diabetes mellitus	NINDS/ADRDA	Model 1: Age Race Educational level Model 2: Age Race Education HTN Total cholesterol Smoking Alcohol use BMI Depression status Ankle-brachial index Stroke	HR (95% CI) for incident AD: Model 1: DM only: 1.45 (0.89 to 2.37) APOE e4 only: 2.61 (1.93 to 3.54) Both: 4.53 (2.47 to 8.30) Model 2: DM only: 1.62 (0.98 to 2.67) APOE e4 only: 2.50 (1.84 to 3.40) Both: 4.99 (2.70 to 9.20)
Xu et al., 2009[96]	Community cohort (1248) Registered inhabitants of Kungs-holmen district, Stockholm, Sweden ≥75 years	Mean 5.1 years. Maximum 10.5 years	Diabetes mellitus	NINDS/ADRDA	Model 2: Age Sex Education Baseline MMSE score APOE genotype Survival BMI BP	Risk of AD (HR [95% CI): Non-diabetic: 1 (reference) Borderline DM: 1.87 (1.11 to 3.14) Diabetics with random glucose: < 7.8 mmol/L: 0.34 (0.05 to 2.43) 7.7-11 mmol/L: 1.26 (0.46 to 3.62) ≥ 11 mmol/L: 1.08 (0.4 to2.95) Undiagnosed DM: 3.29 (1.2 to 9.01) Risk of AD with stroke (HR [95% CI]): Non-diabetic: 1 (reference) Borderline DM: 1.93 (0.59 to 6.28) Undiagnosed DM: 3.75 (048 to 4.55)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
						Risk of AD without vascular comorbidities (HR [95% CI): Non-diabetic: 1 (reference) Borderline DM: 2.85 (1.29 to 6.3) Undiagnosed DM: 4.74 (1.08 to 18.46)

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; BMI = body mass index; BP = blood pressure; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; HTN = hypertension

Metabolic syndrome. We identified two longitudinal, prospective studies that examined the association between metabolic syndrome and incident AD (Table 13).[97,98] Both studies were conducted in the United States and together they involved a total of 5603 subjects. Both studies recruited older adults from the community and used NINCDS-ADRDA criteria to establish a diagnosis of AD. Time between screening and followup ranged from 4.4 to 28 years, and the age range for the studies was comparable (mean 76 versus 78 years). Muller et al.,[98] in the Northern Manhattan study, defined the metabolic syndrome according to National Cholesterol Education Program 3rd Adult Treatment Panel Guideline (NCEP-ATPIII), and Kalmijn et al.,[97] in the Honolulu-Asia Aging Study (HAAS), used a novel definition (described below). The NCEP-ATPIII criteria require at least three of the following for a diagnosis of metabolic syndrome:

1) Waist measurement > 88 cm for women or > 102 cm for men.
2) Hypertriglyceridemia (≥ 150 mg/dL [≥ 1.69 mmol/L]).
3) Low high density lipoprotein (HDL; men < 40 mg/dL [< 1.03 mmol/L]); women < 50 mg/dL [< 1.29 mmol/L]).
4) High blood pressure (systolic blood pressure [SBP] ≥ 130 mmHg; diastolic blood pressure [DBP] ≥ 85 mmHg) or currently using an antihypertensive medication.
5) High fasting glucose (≥ 110 mg/dL [≥ 6.10 mmol/L]) or currently using anti-diabetic medication (insulin or oral agents).

In contrast, HAAS defined metabolic syndrome as the sum of seven factors – increased body mass index (BMI), elevated total cholesterol, elevated triglycerides, elevated DBP and SBP, elevated random post-load glucose, and increased subscapular skinfold thickness – expressed as the individual's z score for that risk factor (calculated as the value compared to the total population, assuming a normal distribution [-4 SD to +4 SD]; scores ranged between -12.8 to 13.4, with higher scores indicative of the presence of more risk factors).[97]

The variation in definition of metabolic syndrome makes it difficult to compare results between studies. Comparisons are further limited because of sex and ethnic differences between the two studies. The Northern Manhattan population[98] was predominantly female (67 percent), 39 percent Caribbean Hispanic, 31 percent African-American, and 30 percent white, while HAAS[97] was restricted to Japanese-American men. Fifty-five percent of the participants in the Northern Manhattan study had metabolic syndrome, and 29 percent of the HAAS participants had more than two elevated risk factors of the seven examined. Both studies adjusted for important confounders, such as age, sex, education, and baseline cognitive performance. Muller et al.[98] reported baseline differences between participants with and without metabolic syndrome; subjects with metabolic syndrome were more likely to be female, Hispanic, smokers, and less educated. There was, however, no difference in the risk of developing AD (RR 0.9; 95 percent CI 0.6 to 1.3). Analysis of the components of metabolic syndrome revealed that only diabetes was associated with a statistically significant increase in total dementia (HR 1.6; 95 percent CI 1.2 to 2.2), but the risk for AD did not reach statistical significance (HR 1.4; 95 percent CI 1.0 to 2.1). The RR for AD per 1 unit increase in z-score sum of metabolic risk factors in HAAS was 1.0 (95 percent CI 0.94 to 1.06), and for AD with cerebrovascular disease 1.04 (0.95 to 1.15).[97] Investigators also divided z-scores into quartiles and found that there was a trend toward increased risk of dementia (all subtypes) in subjects assigned to quartiles 2, 3 and 4, but data were not presented for AD.

In summary, metabolic syndrome, using two different diagnostic criteria, is not associated with a higher risk of AD. These conclusions are limited by the small number of published studies, differences in the study populations, and the lack of uniform criteria used to diagnose metabolic syndrome. Additional analysis of subsets of risk factors included in metabolic syndrome may provide better insight into the validity of metabolic syndrome as a clinically valid construct for predicting dementia risk.

Table 13. Metabolic syndrome and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Kalmijn et al., 2000[97]	Community cohort (3770)	28 years 82 AD	Metabolic syndrome, defined by the sum of Z scores (-4 to +4 SD, with mean 0) for each of 7 factors (see text, above, for details)	NINCDS-ADRDA	Age Sex Education Additional adjustment for occupation, alcohol consumption, smoking, BP medication, and years of childhood in Japan did not appreciably alter estimates of risk	OR 1.0 (95% CI 0.94 to 1.06) per 1 unit increase in metabolic syndrome z score
Muller et al., 2007[98]	Community cohort (1833)	5.9 (1.6) years 147 AD	Metabolic syndrome according to National Cholesterol Education Program 3rd Adult Treatment Panel Guideline (NCEP-ATPIII; (see text, above, for details)	NINCDS-ADRDA	Age Sex Race Education Ethnic group APOE allele Smoking	HR 0.9 (95% CI 0.6 to 1.3)

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; BP = blood pressure; CI = confidence interval; HR = hazard ratio; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; SD = standard deviation

Hypertension. We did not identify any good quality systematic reviews evaluating hypertension and risk of developing AD. Our independent search identified 11 eligible publications,[99-109] describing 10 different cohort studies that examined the association between hypertension and incident AD. These studies are summarized in Table 14; detailed evidence tables are provided in Appendix B. Seven studies were derived from community cohorts in the United States, of which two dealt specifically with subjects of Japanese descent.[99,102] Subjects from the remaining three cohorts were from Finland, Sweden, and Canada. More than 18,700 subjects were included, with 1511 incident cases of AD. Followup ranged from 5 to 27 years. All studies reported good procedures for determination of AD outcome. Only four studies[102,106-108] reported results adjusted for antihypertensive use. Two other studies[103,109] did check for interactions between antihypertensive medications and hypertension and stated that the change to reported results was minimal.

Definitions of hypertension varied. Two of the studies used self-reported hypertension to establish exposure.[104,105] Bias could be introduced by the subjects who are unaware of their hypertension, decreasing the likelihood of detecting an association. Neither study found an association between reported hypertension and incident AD.

When SBP > 140 mmHg was used as a definition,[99,101,106,107] the results were not statistically significant except for a single study[101] that reported an adjusted OR of 1.97 (95 percent CI 1.03 to 3.77) from a Scandinavian cohort (FINMONICA). An analysis of the HAAS cohort (discussed below) did find an association between never-treated hypertension, defined at 140 mmHg and compared to SBP < 120 mmHg, with non-specific dementia. When hypertension was defined as a SBP > 160 mmHg,[100,102,103,107] only one of four studies[100] found a significant result, again in an analysis of the FINMONICA cohort. The FINMONICA cohort measured blood pressure in mid-life, 15 years prior to cognitive testing.

The Religious Orders Study[108] followed a cohort of retired catholic clergy and used blood pressure as a continuous variable. There was no relationship between SBP or DBP and incident AD. Results from this highly educated cohort may not be generalizable to others, as the mean SBP was 134 (64 percent had SBP < 140 mmHg), and the mean DBP was 75 (93 percent had DBP < 90 mmHg).

It is possible that all the cohorts formed later in life[99,103-108] had a selection bias in that if hypertension predisposes to AD and to death, those subjects with hypertension would have selectively died prior to cohort formation. By contrast, the FINMONICA cohort[100,101] was followed for 21 years, and the HAAS cohort[102] for 27 years.

Measures of DBP also did not show robust associations with incident AD. Low DBP (< 70 mmHg) was examined in the Kungsholmen cohort and was significantly associated with incident AD (RR 1.9; 95 percent CI 1.2 to 3.0).[107] High DBP was examined as a risk factor in six studies (seven papers)[100-103,107-109] and was not found to have a significant association with incident AD with the exception of subgroups of the HAAS cohort. The HAAS cohort[102] was formed from the Honolulu Heart Program (1965 to 1971), when many hypertensive patients were not treated. Investigators found significantly elevated odds ratios for AD in those with untreated high DBP (OR 4.47; 95 percent CI 1.53 to 13.09), but not untreated high SBP (OR 1.22; 95 percent CI 0.37 to 4.04). The HAAS cohort is distinguished by having the longest followup of these studies, with a mean of 27 years. In other analyses of the HAAS cohort,[110] non-specific dementia was associated with never-treated hypertension, as defined by SBP > 140 mmHg (and compared to SBP < 120 mmHg), with a HR or 2.66 (95 percent CI 1.51 to 4.68).

In summary, in the cohorts described here, the association between blood pressure and incident AD was significant in only one cohort (the FINMONICA cohort[100,101]), with untreated diastolic hypertension significantly associated with incident AD in one other population (the HAAS cohort[102]). These two populations, however, were followed for a considerably longer period of time than the other cohorts.

Table 14. Hypertension and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Borenstein et al., 2005[99] Kame	Community cohort (1859)	6.0 years (2.7) 90 cases probable AD	Directly measured and self-reported HTN Analysis seems to be based on measured BP, but also ran self-reported history of HTN as a categorical variable	NINCDS-ADRDA DSM	Age Race Sex APOE e4 Educational level Baseline cognitive status Developmental risk factors Vascular risk factors	For subset with no e4 and SBP ≥ 140 mmHg, HR for incident AD 1.79 (95% CI 0.82 to 3.8)
Kivipelto et al., 2001[100] and Kivipelto et al., 2005[101] FINMONICA and others	Community cohort (1449)	Mean 21 years (4.9) Range 11 to 26 years 48 AD	2001 study: Direct measure of BP (and cholesterol) SBP definitions (mmHg): Normal < 140 Borderline 140 to 159 High > 159 DBP definitions (mmHg): Normal < 90 Borderline 91 to 94 High > 94 2005 reanalysis: SBP > 140 used to define HTN	NINCDS-ADRDA DSM	2001 study: Age BMI Education History of MI History of cardiovascular symptoms Smoking Alcohol use 2005 reanalysis: Apparently no adjustment	2001 study: OR (95% CI): Mid-life borderline SBP: 2.1 (0.8 to 5.0) Mid-life high SBP: 2.8 (1.1 to 7.2) Mid-life borderline DBP: 1.4 (0.6 to 3.5) Mid-life high DBP: 1.7 (0.8 to 3.6) 2005 reanalysis: Independent OR (95% CI) for SBP > 140 mmHg: 1.97 (1.03 to 3.77)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Launer et al., 2000[102] Honolulu Heart Program (HAAS)	Community cohort (analytic sample of 3703)	Mean 27 years 118 AD (197 demented, 79 vascular dementia)	Direct measurement of BP and self-report of antihypertensives SBP ≥ 160 mmHg on at least two exam dates to meet criteria for HTN; otherwise, was considered mixed Same for DBP ≥ 95	NINCDS-ADRDA DSM	Age (at the fourth exam) Education APOE Smoking (through exam 3) Alcohol use (at exam 3) CVA CHD Subclinical atherosclerosis Antihypertensive use	High SBP (1965) and AD (1991-3): OR 1.22 (95% CI 0.37 to 4.04) untreated High SBP (1965) and AD (1991-3): OR 0.56 (95% CI 0.20 to 2.15) treated Among untreated, high DBP (OR 4.47; 95% CI 1.53 to 13.09) and borderline DBP (3.49; 1.28 to 9.52), but not mixed DBP (1.33; 0.54 to 3.26), associated with AD Among treated, no association between DBP and AD: High DBP (OR 0.14; 95% CI 0.02 to 1.17), borderline DBP (0.71; 0.17 to 3.00); mixed DBP (1.35; 0.49 to 3.69) For dementia overall (not specifically AD), DBP (high and borderline) associated with dementia in untreated but not treated group For dementia overall (not specifically AD), high SBP, but not borderline or mixed, associated with dementia in untreated but not treated group
Li et al., 2007[103] Adult changes in thought	Community cohort (2356)	Up to 10 years 204 cases probable AD	Direct measurement of BP at baseline 1994-96 SBP ≥ 160 mmHg	NINCDS-ADRDA DSM	Race (white/nonwhite) Sex Education Presence of at least one APOE e4 allele	For SBP ≥ 160 mmHg, HR (95% CI) for AD: Age 65-74: 1.38 (0.71 to 2.70) Age 75-84: 0.94 (0.62 to 1.42) Age ≥ 85: 0.70 (0.25 to 1.95) HR (95% CI) for AD with DBP ≥ 90 mmHg compared to DBP < 80 mmHg: Age 65-74: 0.82 (0.29 to 2.35) Age 75-84: 0.73 (0.34 to 1.59) Age 85+: No cases HR (95% CI) for AD with DBP 80-89 mmHg compared to DBP < 80 mmHg: Age 65-74: 1.71 (0.98 to 2.97)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
						Age 75-84: 0.96 (0.63 to 1.47) Age 85+: 1.58 (0.58 to 4.29) Not significant in any age group
Lindsay et al., 2002[104] CSHA	Community cohort (4615)	5 years 194 AD	Not completely clear, but apparently history of HTN came from self-administered questionnaire completed by cognitively normal subjects	NINCDS-ADRDA	Age Sex Education	OR 0.88 (95% CI 0.62 to 1.27)
Luchsinger et al., 2005[105] Northern Manhattan	Community cohort (1138)	5.5 years (3.2) 246 probable or possible AD	Self-reported HTN	NINCDS-ADRDA	Age Race Sex Educational level Baseline cognitive status Vascular disease Lipid values BMI	RR for probable AD: 1.5 (95% CI 0.9 to 2.6) RR for both probable and possible AD: 1.5 (0.9 to 2.4)
Posner et al., 2002[106] Washington Heights – Inwood Columbia Aging Project	Community cohort (1249)	Up to 7 years 157 AD	Direct measurement and self-report SBP > 140 mmHg	NINCDS-ADRDA	Age Race Sex Educational level DM Heart disease (MI, CHF, angina) Antihypertensive use	AD with a history of HTN: RR 0.8 (95% CI 0.6 to 1.1) Treatment of HTN did not affect risk estimates for AD: No treatment: RR 0.96 (95% CI 0.6 to 1.5) Treatment: RR 0.86 (0.6 to 1.5)
Qiu et al., 2003[107] Kungsholmen	Community cohort (966)	Mean 5.7 years Range 0.1 to 8.2 years	Direct measurement of BP and self-report of medications	DSM	Age Race Sex Educational level Baseline MMSE	RR (95% CI): SBP 140-159: 1.3 (0.8 to 2.0) SBP ≥ 160: 1.4 (0.9 to 2.2) DBP ≥ 90: 1.0 (0.7 to 1.4) DBP < 70: 1.9 (1.2 to 3.0)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
		204 AD	SBP ≥ 140 mmHg		Vascular disease (heart disease, CVD, DM) APOE genotype SBP DBP Antihypertensive use	Antihypertensive drug use: 0.6 (0.5 to 0.9) Authors state: "Compared with those with no use of antihypertensive drugs, no APOE e4 and systolic pressure < 140, the adjusted relative risks of AD were 3.2 (1.6 to 6.4) for subjects with e4 and systolic pressure > 140 but no use of drugs, and 1.5 (0.7 to 3.2) for persons with e4, systolic pressure > 140 and use of drugs."
Shah et al., 2006[108] Religious Orders Study	Community cohort – sample of retired clergy (824)	Mean of 6.5 annual exams 151 AD	Direct measurement of BP BP used as a continuous variable	NINCDS-ADRDA	Age Sex Education APOE e4 Antihypertensive use	In a fully adjusted model (presence of APOE e4, use of antihypertensive meds), a "null relationship persisted," but results were not shown. Adjusting for age, sex, and education, the RR of a 1-mmHg increase in SBP was 0.99 (95% CI 0.99 to 1.00) and for DBP 1.0 (0.99 to 1.01). Further analyses, using history of HTN, quadratic terms for SBP and DBP, JNC VII categories of HTN, and sitting BP only, showed no association with incident AD
Morris et al., 2001[109] Boston EPESE	Community cohort (634)	2 to 13 years 99 AD	Direct measurement of blood pressure Analysis with blood pressure as a continuous and as a categorical variable	NINCDS-ADRDA	Age Sex Education APOE Clinical stroke Heart disease History of HTN DM BMI	OR (95% CI) for AD, BP measured 4 years prior to diagnosis: SBP 140-149: 0.29 (0.11 to 0.81) SBP ≥ 160: 0.22 (0.07 to 0.68) DBP ≥ 90: 0.79 (0.24 to 2.64) OR (95% CI) for AD, BP measured 13 years before diagnosis: SBP ≥ 160: 1.13 (0.24 to 5.37) DBP ≥ 90: 1.56 (0.46 to 5.32)

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; APOE e4 = e 4 allele of the apolipoprotein E gene; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; CVA = cerebrovascular accident; CVD = cardiovascular disease; DBP = diastolic blood pressure; DM = diabetes mellitus; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; HTN = hypertension; JNC VII = The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; MI = myocardial infarction; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; RR = relative risk; SBP = systolic BP

Hyperlipidemia. We identified one good quality systematic review examining total cholesterol as a possible risk factor for AD.[40] Eight included cohort studies, involving 14,331 subjects, examined the association between incident AD and total cholesterol. Three of the studies used cholesterol measured in mid-life, one used the average of multiple cholesterol measurements over 30 years, and four used cholesterol measured in later life; for this reason, the studies were considered too heterogeneous to combine in a single analysis. Followup ranged from 4.8 to 29 years, with a mean of approximately 13 years.

Four studies examined cholesterol as measured in mid-life as it relates to incident AD. One looked at the Framingham cohort.[111] Cholesterol levels were averaged over the time of the study. No association was found between cholesterol measured in this way and incident AD. Another study[112] found that a decreasing cholesterol level from mid- to late life was associated with increased risk of AD ($\beta = -0.33$; $p = 0.03$). Two studies found that high cholesterol in mid-life was associated with an increased risk of AD. Kivipelto et al.[113] found that, in the FINMONICA (Finnish Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) and North Karelia Project cohort, followed for a mean of 21 years (range 11 to 26 years), cholesterol ≥ 6.5 mmol/L (251 mg/dL) in mid-life was associated with an OR of 2.8 (95 percent CI 1.2 to 6.7) for incident AD in late life. Notkola et al.[114] followed up 444 survivors from a cohort formed in 1959, checked after 5 to 30 years, and found an OR of 3.1 (1.2 to 8.5) for an average cholesterol ≥ 6.5 mmol/L for measured cholesterol in 1959, 1964, 1969, and 1974, when the cohort was mid-life.

Four studies looked at late-life cholesterol and AD. Three studies were considered similar enough for fixed-effect meta-analysis.[115-117] Combined sample size for these three was 10,195 controls and 599 cases of incident AD. No difference was found between the lowest quartile of total cholesterol and any of the other quartiles in the incidence of AD. The relative risk (RR) between first and fourth quartile was 0.85 (95 percent CI 0.65 to 1.12; $z = 1.17$; $n = 5526$; $p = 0.24$). Yoshitake et al.[118] included both prevalent and incident cases of AD in their analysis and found that for each increase of one standard deviation in total cholesterol the relative risk for AD was 1.1 (0.80 to1.51).

In summary, based on this systematic review, there is evidence to suggest that hypercholesterolemia in mid-life is associated with increased risk of AD later. There is no evidence in these studies to suggest that late-life cholesterol levels are related to incident AD. If mid-life but not late-life cholesterol is related to increased risk, then averaging cholesterol over decades of life, as was done with the Framingham cohort, would not be expected to show a relationship.

Our search did not reveal any other prospective cohort studies meeting our inclusion criteria and addressing the relationship between hyperlipidemia and incident AD.

Homocysteine. Our search identified four cohort studies, involving 2662 subjects, evaluating the association between homocysteine and incident AD (Table 15). Two cohorts were from U.S. communities,[119,120] and two were from Western Europe;[57,121] all studies recruited community samples. Three of the four cohorts analyzed frozen plasma from fasting subjects, which may give a better estimate of bioavailable folate than non-fasting samples. The fourth study[121] did not specify whether subjects were fasting. The studies defined increased plasma homocysteine levels differently. Two studies[57,120] compared the highest quartiles of homocysteine in their samples to the lowest quartile, one examined log-transformed homocysteine,[119] and one compared those subjects whose homocysteine doubled over 2.5 years to all others.[121] The duration of followup ranged from 1 to 13 years. Alzheimer's disease was diagnosed using NINCDS-ADRDA criteria;

however, one study[57] relied on telephone or informant interviews, medical records, or death certificates for 15 percent of the sample. All studies adjusted for potential confounders, but two[57,119] had a large number of model variables compared to the number of incident cases of AD, which may decrease the replicability of their results.

Three studies reported adjusted results for baseline homocysteine using approximately the same threshold (> 14 or >15 μmol/L).[57,119,120] We combined these studies using a random-effects model (Figure 3). A test for heterogeneity suggested significant variability among studies (Q statistic = 6.378, p = 0.04, I^2 = 68.6 percent). We examined design features qualitatively and could not explain the variability. Elevated homocysteine levels were not associated with incident AD, but the confidence interval was wide (RR 1.53; 95 percent CI 0.94 to 2.49).

Other classifications of elevated homocysteine found variable associations. For the highest homocysteine quartile (mean homocysteine 27.44 μmol/L), Luchsinger et al.[120] found an increased risk for AD (HR 2.0; 95 percent CI 1.2 to 3.5). However, this association was no longer statistically significant after adjusting for age, sex, education, APOE e4 status, and history of stroke (HR 1.3; 95 percent CI 0.8 to 2.3). Blasko et al.[121] evaluated the association between change in homocysteine and incident AD. For subjects whose homocysteine level doubled over 2.5 years, the risk of AD was increased (OR 4.2; 95 percent CI 1.6 to 11). It is not clear how frequently homocysteine levels doubled over the 2.5-year duration of the study, but the wide confidence interval may indicate that a relatively low number were in this group.

In summary, adjusted models in three of the four included cohort studies found an association between increased baseline homocysteine and the development of incident AD. Point estimates for the relative risk varied substantially across studies, from modest (1.3) to large (4.2). However a pooled estimate using a common classification of elevated homocysteine did not reach statistical significance. Homocysteine levels rise with age, renal insufficiency, use of coffee, tobacco, and the sequelae from heavy alcohol use. Differences in the cohorts studied with regard to these factors may have contributed to variable findings, but there were not adequate numbers of studies to evaluate this possibility formally.

Table 15. Homocysteine and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Blasko et al., 2008[121]	Community cohort (487)	2.5 years 90 AD	Fasting plasma homocysteine measure at 2 time points	NINCDS-ADRDA DSM	Age Sex Educational level At least one APOE e4	Homocysteine doubling over 2.5 years for those who converted to AD: OR 4.2 (95% CI 1.6 to 11.0)
Luchsinger et al., 2004[120]	Community cohort (679)	4.7 years 109 AD	Fasting plasma homocysteine	NINCDS-ADRDA DSM	Age Sex Education APOE e4 Stroke	Highest quartile of homocysteine (mean 27.44) compared to the lowest quartile (mean 10.75) had increased risk (unadjusted HR 2.0; 95% CI 1.2 to 3.5). Adjusted HR 1.3 (0.8 to 2.3) for highest vs. lowest quartile; p = 0.37 for trend across quartiles. Homocysteine threshold of > 14, HR for AD: 1.0 (0.7 to 1.5) Including B6, B12, and folate as covariates did not affect results
Ravaglia et al., 2005[57]	Community cohort (816)	3.8 (0.8) years 112 dementia (70 AD)	Fasting plasma homocysteine	NINCDS-ADRDA	Age Sex Education APOE e4 Stroke Creatinine Folate Vitamin B12 Smoking status Diabetes mellitus Hypertension Cardiovascular disease BMI	Homocysteine > 15 µmol/L, adjusted HR for AD: 2.08 (95% CI 1.15 to 3.79) Sensitivity analysis excluding 9 AD cases with neuroimaging showing vascular disease did not affect results
Seshadri et al., 2002[119]	Community cohort (680)	Median 8 years (range 1	Plasma homocysteine	NINCDS-ADRDA DSM	Age Sex	For each 1 SD increase in log-transformed homocysteine, adjusted RR for AD: 1.8 (95% CI 1.3 to 2.5)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
		to 13) 44 AD			Education APOE e4 Stroke Creatinine Folate Vitamins B12 and B6 Smoking status Alcohol use Diabetes mellitus Systolic blood pressure BMI	For homocysteine > 14 µmol/L, adjusted HR 1.9 (1.2 to 3.0)

Abbreviations: AD = Alzheimer's disease; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; BMI = body mass index; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; RR = relative risk; SD = standard deviation

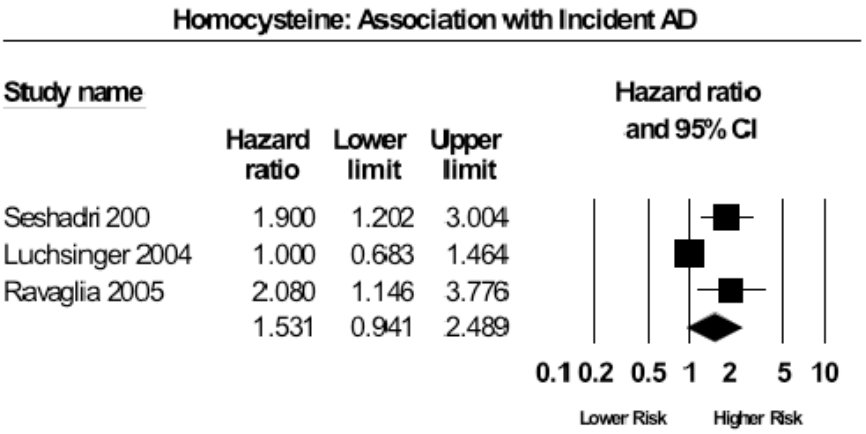

Figure 3. Meta-analysis of three cohort studies on homocysteine and risk of developing AD. Combined estimate is given in bottom row.

Other medical factors. Factors considered under this heading include sleep apnea, obesity, and traumatic brain injury (TBI).

Sleep apnea. We did not identify any good quality systematic reviews or primary studies that evaluated the association between sleep apnea and risk of developing AD.

Obesity. We identified one good quality systematic review that examined the association between various measures of obesity and the development of AD.[47] The review included 10 prospective cohort studies published between January 1995 and June 2007, of which four were conducted in the United States, two among Japanese men (one of which was in Honolulu), two in Sweden, and one each in Finland and France. Prospective cohort studies were selected if the sample size was > 100; followup was ≥ 2 years; exposure was recorded as BMI, obesity/overweight, a measure of central obesity, or a combination; outcomes reported were AD or vascular dementia (VAD), or a combination; and if the outcomes were reported as odds ratio, relative risk, or hazard ratio, or as data from which these measures could be calculated.

Of the 10 eligible studies included in the review, 4 studies involving 15,688 subjects examined the relationship between AD and obesity and were combined in a meta-analysis.[94,101,122,123] The results from the other studies included dementia as a whole or vascular dementia separately, but did not report associations with AD. All participants were ≥ 65 years of age at the time of cognitive testing; however, age at baseline ranged from 40 to 45 years old to more than 77 in some studies. Length of followup ranged from 3.2 to 36 years. All studies measured BMI, and one study also measured change in BMI.[122] Level of covariate adjustment was reported at the individual study level. Although the review included both AD and VAD, both combined and individual analyses were done for the two outcomes, and the RR for AD was reported separately. Study quality for the primary studies was not assessed in this review.

Studies were combined for meta-analysis using a fixed-effect model, as the heterogeneity among the four studies was not statistically significant. A funnel plot that included all studies did not reveal significant publication bias. This was confirmed by two other numerical tests (Egger's regression asymmetry test: - 0.14 ± 0.54, P = 0.791; and Begg-adjusted rank correlation test: z = 0.62; P = 0.533). For the four cohort studies, compared with normal-weight subjects, those who were obese had a higher risk of developing AD (RR 1.80; 95 percent CI 1.00 to 3.29). Analysis

was done to estimate the RR of dementia based on weight status; however, this analysis combined AD and VAD as outcomes.

We identified three additional prospective cohort studies published after the beginning of 2008 which examined the association between obesity and Alzheimer's disease.[124-126] These studies are summarized in Table 16; detailed evidence tables are provided in Appendix B. The first study was conducted in a community in Sweden where 1255 participants who were enrolled in the Kungsholmen Project were followed for 9 years.[124] The two other studies were conducted in the United States, but the population in one of these studies was restricted to those of Japanese ethnicity.[125] The average followup periods in the U.S. studies were 5.9 years[126] and 7 to 9 years.[125] In all three studies, selection bias was minimized by recruiting participants from the community and by excluding those who had dementia at baseline. Two of the three studies compared baseline characteristics by weight,[125,126] while one examined baseline characteristic only by sex.[124] All three studies directly measured weight for the calculation of BMI; one study also considered midlife weight by self-report as an additional risk factor.[126] BMI was categorized into four groups in each study; however, the cut-offs used were slightly different in the studies, as follows: in Fizpatrick et al., underweight (BMI < 20), normal weight (20-25), overweight (25-30), and obese (> 30);[126] in Hughes et al., obese (BMI ≥ 25.0), overweight (23.0-24.9), normal (18.5-22.9), and underweight (< 18.5);[125] and in Atti et al., obese (BMI ≥ 30), overweight (25-29.9), normal weight (20-24.9, reference category) and underweight (< 20).[124] Although all studies assessed both AD and other types of dementia , the investigators conducted a separate analysis for those with AD only as the outcome.

Atti et al.[124] concluded that higher BMI was associated with a lower risk of developing AD; that is, overweight subjects had a lower risk of developing dementia over 9 years (HR 0.66; 95 percent CI 0.50 to 0.88). The other conclusion was that loss of weight is a marker of incipient dementia. Hughes et al. concluded that after controlling for covariates except APOE, higher baseline BMI was associated with a decreased risk of AD (HR 0.56; 95 percent CI 0.33 to 0.97); however, this model was no longer significant after controlling for APOE (HR 0.68; 95 percent CI 0.31 to 1.51). Also, lower decline in BMI was associated with a decrease in risk of incident AD (HR 0.21; 95 percent CI 0.06 to 0.80).[125] Fitzpatrick et al. also concluded that underweight persons (BMI < 20) had an increased risk of dementia (HR 1.62; 1.02 to 2.64), whereas being overweight (BMI_25-30) was not associated (HR 0.92; 0.72 to 1.18), and being obese reduced the risk of dementia (HR 0.63; 0.44 to 0.91) compared with those with normal BMI. In the same study, when the association between midlife BMI and dementia was examined, there was a reversal in the direction of risk, as an increased risk of dementia was found for the obese (BMI > 30) versus those of normal weight (BMI 20-25), adjusted for demographics (HR 1.39; 1.03 to 1.87) and for cardiovascular risk factors (HR 1.36; 0.94 to 1.95).[126]

In conclusion, the meta-analysis published as part of a systematic review found that obesity was associated with an *increased* risk of AD, while all three prospective cohort studies published after the meta-analysis found that that a higher BMI was associated with a *lower* risk of developing AD. These conflicting results could be explained by the differences in age in the different study populations. The reversal of the direction of risk found by Fitzpatrick et al.[126] is interesting, as it implies that BMI does not consistently predict dementia risk across the lifespan, and that this risk might change based on the age of exposure to obesity. Also, decreasing BMI might be a sign of early dementia, as one cannot attribute a causal relationship between decrease in weight and dementia yet.

Table 16. Obesity and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Atti et al., 2008[124]	Community cohort (1255 total; 646 analyzed)	9 years	BMI	DSM III Clinical evaluation by two doctors	MMSE Depression Impaired ADLs Chronic disease before baseline	Overweight subjects had a lower risk of developing dementia over 9 years: HR 0.66 (95% CI 0.50 to 0.88)
Hughes et al., 2009[125]	Community cohort (1836 total; 1478 analyzed)	7 to 9 years	BMI	NINCDS-ADRDA DSM IV	Age Race Sex Educational level Alcohol Smoking Hypertension Hypercholesterolemia Diabetes Angina pectoris Stroke TIA Physical activity APOE genotype	Lower decrease in BMI was associated with decreased risk of AD: HR 0.21 (95% CI 0.06 to 0.80) Higher baseline BMI was significantly associated with a reduced risk of AD: HR 0.56 (0.33 to 0.97). This was not statistically significant after correcting for APOE: HR 0.68 (0.31 to 1.51).
Fitzpatrick et al., 2009[126]	Community cohort (2798)	5.4 years	BMI	NINCDS-ADRDA	Age Race Sex Educational level Baseline cognitive status Cardiovascular and dementia risk	For late life BMI, underweight persons (BMI < 20) had an increased risk of dementia (HR 1.62; 95% CI 1.02 to 2.64), whereas being overweight (BMI 25-30) was not associated (0.92; 0.72 to 1.18) and being obese reduced the risk of dementia (HR 0.63; 0.44 to 0.91) compared with those with normal BMI. However, midlife obesity was associated with increased risk of dementia (HR 1.39; 1.03 to 1.87).

Abbreviations: ADLs = activities of daily living; APOE = apolipoprotein E gene; BMI = body mass index; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; MMSE = Mini-Mental State Examination; SDMT = Symbol Digit Modalities Test; TIA = transient ischemic attack

Traumatic brain injury (TBI). We identified one good quality systematic review that examined the association between traumatic brain injury (TBI) and the development of AD in case-control studies.[46] We did not generally consider case-control studies for this report due to the numerous limitations of such studies compared to cohort studies. However, in the case of TBI, there were few prospective cohort studies that met our eligibility criteria, but meta-analyses have been done using case-control studies. In the general population, TBI is a relatively low prevalence event, meaning that large sample sizes are necessary to have sufficient power to detect an association in general community samples. In addition, TBI is not an exposure that lends itself to RCTs. For these reasons, we decided to include the meta-analyses described here in our review. The review included 15 case-control studies.[127-141] There were a total of 2653 subjects in the combined sample, of which 164 had exposure to TBI and 2489 did not have a reported history of TBI. As expected in case-control studies, the cases were demented at baseline and the controls were not demented. Six of the studies were conducted in the United States, six in European countries, and one each in Canada, Australia, and China. Studies were included if their definition of TBI required loss of consciousness; they used either individual or group matching of cases and controls; they used NINCDS-ADRDA or DSM diagnostic criteria; they used predefined inclusion criteria for controls to rule out the possibility of dementia; data on TBI were collected from informants for both cases and controls (symmetrical data collection); and the TBI occurred prior to onset of AD. The authors did not conduct a structured quality assessment of the studies reported in this systematic review; however the inclusion/exclusion criteria provided a limited indirect assessment of quality. The review did not provide information on the length of followup, followup rates, or the analytical covariates used in the studies. Exposure to TBI with loss of consciousness was determined by proxy-report for both cases and controls. All studies used the DSM and/or NINDS/ADRDA diagnostic criteria. Standard χ^2 tests using a p-value of 5 percent were used to examine heterogeneity; results of these analyses showed no significant heterogeneity was present (actual p values were $p \geq 0.58$). Studies were combined using fixed-effect meta-analyses since there was no evidence of heterogeneity. The results from these analyses are shown in Table 17.

Table 17. Traumatic brain injury and risk of developing AD – results from case-control studies reviewed by Fleminger et al., 2003[46]

Studies analyzed	Odds Ratio (95% CI)
All studies (n = 15 studies)	1.58 (1.21 to 2.06)
Females (n = 7 studies)	0.91 (0.56 to 1.47)
Males (n = 5 studies)	2.29 (1.47 to 3.58)
Studies with information on time interval from TBI to AD onset (n = 10 studies)	1.56 (1.12 to 2.18)

Abbreviations: AD = Alzheimer's disease; CI = confidence interval; TBI = traumatic brain injury

The authors had planned to assess the association between TBI and APOE genotype as risk factors for AD, but they were unable to do so because only two of the included studies reported APOE genotype. Publication bias was not assessed formally, but the authors did attempt to assess for recall bias, a potential major weakness of case-control studies on individuals with dementia. When limiting the analyses to those cases and controls for whom the informant type was the same (e.g., informants were spouses in both groups), the association weakened slightly

and became statistically insignificant (OR 1.42; 95 percent CI 0.75 to 2.67). This finding suggests that differential quality of informants for cases and controls in some studies may have resulted in a slight overestimate of the association between TBI and AD in the analyses combining all studies. Quality ratings of the studies were not provided, but the selection criteria may have increased the likelihood that higher quality studies were included in the review. However, it is noted that some studies had small sample sizes, and one study limited the cases of AD to those with onset prior to age 65,[134] potentially limiting the generalizability of the results. The authors concluded that TBI may confer an increased risk of AD in males only. They also advised that future studies should use medical records to document head injury and should use population-based cohort designs to avoid the limitations associated with case-control studies.

Due to the limitations inherent in case-control studies, we supplemented the above-described systematic review[46] with a search for cohort studies. This search identified two eligible prospective cohort studies[104,142] and one retrospective cohort study.[143] These studies are summarized in Table 18; detailed evidence tables are provided in Appendix B. Two of the studies drew samples from the community,[104,142] and one drew its sample from military hospitalization records in the early 1940s;[143] this latter study included both community residents and institutionalized individuals. One study was conducted in the United States,[143] one in Canada,[104] and the third in Europe.[142] Length of followup ranged from 2 to approximately 55 years. Two studies used self-report history of TBI, and one study used military medical records at baseline to characterize exposure. For two of the studies,[142,143] the definition of TBI required loss of consciousness or post-traumatic amnesia associated with the injury, but the third study[104] did not include this requirement. For all three studies, individuals were non-demented at baseline. Two of the studies used sample selection methods to minimize selection bias;[104,142] due to the retrospective nature of the third study,[143] it only partially met criteria for sample selection methods that minimize selection bias. Only one of the studies[143] compared baseline characteristics to assess differences between exposed and unexposed. All three studies used standard criteria for the diagnosis of AD. Only one study[143] reported that the cognitive diagnoses were assigned blind to exposure status; the other two did not report this information. Analyses were appropriate and controlled for relevant potential confounders, but none of the studies reported a priori sample size calculations.

Two of the studies found that risk of AD did not increase in relation to a history of TBI.[104,142] The third study reported that TBI was associated with increased risk of AD, and that there was a dose-response effect, with the risk being due to those with moderate and severe injuries.[143] This latter study used an all-male sample. One of the other studies investigated potential differences by sex and found no differences in the association between TBI and AD for males and females.[142] The inconsistency in results across studies may be due to the differences in the method of exposure ascertainment (i.e., self-report of lifetime history of exposure versus abstracted information from medical records) and to differences in the severity of traumatic brain injuries based on the sample characteristics (i.e., sample made up entirely of WWII veterans versus samples with limited number of war veterans). Two of the studies investigated the interaction between TBI and the APOE e4 allele on risk of AD. One study found no interaction effect.[142] The other reported progressively larger hazard ratios with increasing numbers of e4 alleles, but the results did not reach statistical significance, possibly due to the relatively small sample size.[143]

As noted above, the methodological differences in the studies provide plausible reasons for the differing results. The systematic review of case-control studies found an association between

TBI and AD in males only, with the OR for males exceeding 2.0 providing some support for the robustness of the result. The one cohort study with an all-male sample also reported that TBI increased risk of AD.[143] The latter study used medical records from the 1940s to document exposure, thus avoiding reliance on self-report of lifetime history of injury. This study also reported a concordance rate of about 65 to 69 percent between documented TBI in military medical records and subsequent self- or proxy report of a history of TBI, suggesting that reliance on self- or proxy report may result in marked exposure misclassification. None of the studies could adequately assess whether there is a synergistic effect between the APOE e4 allele and TBI in altering risk of AD.

In summary, there is some evidence that TBI, even in early adulthood, may increase risk of AD years later. For those studies that reported an association between TBI and increased risk of AD, one study had an all-male sample, and the other found the association only in males. This potential gender-specific effect may be attributed to males being exposed to more severe TBIs given the dose-response association reported by one study.[143] Further confirmation of this finding is needed using sources such as medical records to document exposure to TBI.

Table 18. Traumatic brain injury and risk of developing AD – cohort studies

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Mehta et al., 1999[142]	Community cohort (6645)	Mean 2.1 (0.8) years 91 AD cases	Self-report TBI history	NINCDS-ADRDA DSM	Age Sex Education	Relative risk for AD in those with TBI: 0.8 (95% CI 0.4 to 1.9)
Lindsay et al. , 2002[104]	Community cohort (3745 analytical sample)	5 years 179 AD cases	Self-report TBI history	NINCDS-ADRDA DSM	Age Sex Educational level	Odds ratio for AD in those with TBI: 0.87 (95% CI 0.56 to 1.36)
Plassman et al., 2000[143]	Clinical cohort (retro-spective) (1776)	~ 55 years 35 AD cases	TBI history from military medical records and self-report	NINCDS-ADRDA DSM	Age Educational level APOE	Risk for AD in those with TBI: 2.01 (95% CI 1.03 to 3.91) Risk (95% CI) for AD increased with severity of head injury: Mild TBI: 0.76 (0.18 to 3.29) Moderate TBI: 2.32 (1.04 to 5.17) Severe TBI: 4.51 (1.77 to 11.47)

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; DSM = Diagnostic and Statistical Manual of Mental Disorders; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; TBI = traumatic brain injury

Psychological and emotional health. Factors considered under this heading include depression, anxiety, and resiliency.

Depression. We identified one good quality systematic review that examined the association between depression and the development of AD.[45] The review included 11 cohort studies (95,104 subjects) and 9 case-control studies; 6 were from the United States, 5 from European countries, and 1 from Canada. Studies were selected that had sufficient data to calculate an odds ratio (OR) for risk of AD or AD-like dementia, had a control group for comparison, and made a clinical diagnosis of depression and AD. Study quality for cohort designs was fair; 4 of 11 had limitations in assessment of exposure,[104,144-146] and 5 of 11 had important limitations in assessment of AD.[144-148] Length of followup and level of covariate adjustment were not reported at the individual study level. Studies were classified as those using specific depression criteria (e.g., ICD or DSM) to ascertain exposure and studies using symptoms consistent with major depressive disorder but without specific criteria. Several studies used hospitalization for depression as an indicator of clinical depression, and these studies may not be applicable to individuals with milder depression. Studies were further classified into those assessing AD and AD-like dementia outcomes with structured criteria such as NINCDS-ADRDA and those using a description of diagnostic criteria for AD or AD-like dementia but without structured criteria.

Included studies were combined using a random-effects model. A test for heterogeneity suggested significant variability between studies that persisted when the analysis was limited to studies using a cohort design ($p = 0.02$). An I^2 was not reported. A funnel plot suggested possible publication bias. For the 11 cohort studies, depression was associated with a statistically significant increased risk of AD (OR 1.90; 95 percent CI 1.55 to 2.33). An influence analysis that recalculated the summary OR iteratively, removing one study with each iteration, yielded ORs ranging from 1.81 (95 percent CI 1.45 to 2.24) to 2.03 (1.71 to 2.41), suggesting that no single study had a large effect on the estimate of association. A meta-regression analysis showed a positive association between the interval between depression diagnosis and risk of AD, suggesting that depression is a risk factor for AD, rather than a prodrome of the disease.

The authors conducted stratified analyses for prospective versus retrospective study designs and specific or non-specific exposure and outcome assessments (Table 19). These analyses showed a statistically significant association for all subgroups. In the four studies using the most rigorous criteria for depression and AD diagnosis, the pooled OR was 2.23 (95 percent CI 1.71 to 3.09).

Table 19. Depression and risk of AD – results from stratified analyses by Ownby et al., 2006[45]

Stratification of analysis	Odds ratio (95% CI)
Cohort studies (n = 11)	1.90 (1.55 to 2.33)
Case-control studies (n = 9)	2.03 (1.73 to 2.38)
Prospective cohort studies (n = 4)	1.78 (1.16 to 2.73)
Retrospective cohort studies (n = 7)	2.11 (1.82 to 2.45)
Specific depression criteria	2.23 (2.00 to 2.48)
No specific depression criteria	1.85 (1.58 to 2.17)
Structured AD criteria	1.91 (1.62 to 2.26)
No structured AD criteria	2.22 (1.98 to 2.49)

Abbreviations: AD = Alzheimer's disease; CI = confidence interval; n = number of subjects

The authors concluded that depression may confer an increased risk for developing AD later in life.

We identified five additional eligible studies involving 4961 subjects published since the beginning of 2005 (Table 20). Two studies were conducted in the United States, one in Canada, one in the United States and Canada, and one in Europe. Four prospective cohort studies recruited older adults without dementia from the community and used NINCDS-ADRDA criteria to establish AD over 5 to 6 years of followup. One study evaluated the association between depressive symptoms and incident AD in subjects with amnestic MCI recruited for a 3-year trial of vitamin E or donepezil.[149] All studies assessed current depressive symptoms at baseline using a validated instrument. The significance of such a single assessment for depressive symptoms is uncertain. Two studies[150,151] went further and established a clinical history of depression requiring medical attention. All studies adjusted for some important confounders, but other potentially important confounders, such as comorbid psychiatric conditions, were not evaluated. Geerlings et al.[151] found an association between depression requiring medical attention if onset was before age 60 (HR 3.7; 95 percent CI 1.43 to 9.58), but not for late-onset depression (HR 1.71; 95 percent CI 0.62 to 4.74). The study reporting a "history of depression" did not find an association with AD at 5 years (OR 1.5; 95 percent CI 0.49 to 4.63), but the precision of the estimate was poor due to few incident cases.[150] One study[22] found an interaction between APOE e4 and depressive symptoms, but the only other study evaluating this interaction found no significant effect.[149] All studies found an association between significant depressive symptoms at baseline and incident AD.

In summary, a previous systematic review found an association between clinical depression and incident AD that was robust to subgroup analyses by study design features. Despite variability in depression assessment, ranging from a self-reported history to hospitalization, the association with incident AD was reasonably consistent. However, publication bias may have inflated the summary estimate of effect. Since publication of the systematic review, five additional studies found an association between current depressive symptoms and incident AD; one of the four additional studies found an association for early onset clinical depression. Collectively, these observational studies suggest an association between a history of depression and incident AD.

Table 20. Depression and risk of developing AD – recent cohort studies

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Gatz et al., 2005[150]	Community cohort (766)	5 years 36 AD	CES-D ≥ 16; history of depression	NINCDS-ADRDA	Age Sex Education	OR 2.75 (95% CI 1.04 to 7.24)
Geerlings et al., 2008[151]	Community cohort (563)	5.9 (1.6) years 33 AD	CES-D ≥ 16; history of depression requiring medical attention	NINCDS-ADRDA	Age Sex Education Baseline cognition Memory complaints	HR 2.46 (95% CI 1.15 to 5.26)
Irie et al., 2008[22]	Community cohort (2350)	6 years Number of AD cases NR	11-item CES-D ≥ 9	NINCDS-ADRDA	Age Education Smoking DM BMI ABI Cholesterol Memory complaints	HR 2.9 (95% CI 1.4 to 5.9) HR 13 (95% CI 4.3 to 39.5) for both CES-D ≥ 9 and APOE e4
Lu et al., 2009[149]	Cohort derived from RCT of donepezil/ vitamin E in those with MCI (756)	3 years 34 AD at 1.7 years	BDI	NINCDS-ADRDA	Age Baseline cognition Treatment group APOE	HR 1.03 (1.01 to 1.06)
Luchsinger e al., 2008[152]	Community cohort	5.1 (3.3) years	HDRS	NINCDS-ADRDA	Age Sex Race Educational level APOE e4 Vascular risk factors	HDRS 1 to 9, HR 2.3 (1.0 to 5.3) HDRS > 9, HR 3.0 (1.2 to 7.9)

Abbreviations: ABI = ankle-brachial index; AD = Alzheimer's disease; APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; BDI = Beck Depression Inventory; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale (range 0-60; 11-item version scored 0-33); CI = confidence interval; DM = diabetes mellitus; HDRS = Hamilton Depression Rating Scale (range 0 to 51; 17-item version); HR = hazard ratio; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; NR = not reported; OR = odds ratio

Anxiety. We did not identify any systematic reviews or primary studies that evaluated the association between anxiety disorders and incident AD.

Resiliency. We did not identify any systematic reviews or primary studies that evaluated the association between psychological resiliency and incident AD.

Medications. Prescription and non-prescription drugs considered under this heading include statins, antihypertensives, anti-inflammatories, gonadal steroids, cholinesterase inhibitors, and memantine.

Statins. Our search identified six eligible studies examining the association between 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) and incidence of AD. Five were cohort studies (17,840 subjects; described in six publications),[153-158] and one was a secondary analysis of data from an RCT (2223 subjects).[159] No recent good quality systematic reviews were identified. All studies drew samples from the community, five in the United States and one in The Netherlands, and then followed patients from 3 to 17 years. All but one study[153] selected samples using methods to minimize selection bias and baseline differences between exposed and unexposed groups. Statin use was determined only at baseline – a crude measure of exposure – in two studies.[153,158] AD outcomes were assessed using structured criteria, but only two studies reported assessments that were blind to exposure status.[154,158] Analyses were appropriate and controlled for confounding, but only one study conducted an a priori sample size calculation.[155] Study characteristics are summarized in Table 21.

Table 21. Statins and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Arvanitakis et al., 2008[153]	Community cohort (929)	1-12 years 191 AD	Statin use at baseline; bottles inspected	"CERAD approach"	Age Sex Education	Adjusted HR (95% CI): 0.91 (0.54 to 1.52)
Haag et al., 2009[154]	Community cohort (6992)	Mean 9.2 years 464 AD	Any statin during study; pharmacy records	NINCDS-ADRDA	Age Sex Education Smoking BMI Cholesterol DM SBP Cardiovascular disease Cerebrovascular disease Other lipid-lowering agents	Adjusted HR (95% CI): 0.57 (0.37 to 0.90)
Li et al., 2004[155] and Li et al., 2007[156]	Community cohort (2581)	17 years 261 AD	At least 2 consecutive fills during 6 months; pharmacy records	NINCDS-ADRDA	Age Education APOE Other lipid-lowering agents	Adjusted HR (95% CI): 0.82 (0.46 to 1.46)
Rea et al., 2005[157]	Community cohort (2798)	Mean 6 years 396 AD	< 1 year, 1-3 years, > 3 years; bottles inspected annually	NINCDS-ADRDA	Age Sex Education Alcohol use CHD status Stroke status Baseline MMSE	Adjusted HR (95% CI): 0.87 (0.44 to 1.72)
Sparks et al., 2008[159]	Community – secondary analysis of RCT (2223)	4 years 24 AD	Statin at all visits, > 2 but less than all, or < 33% of visits; self-report	NINCDS-ADRDA	Age Sex Education APOE	Adjusted HR (95% CI): 0.33 (0.11 to 0.98)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Zandi et al., 2005[158]	Community cohort (4540)	3 years 102 AD	Any use at baseline; self-report	NINCDS-ADRDA	Age Sex Education HTN DM APOE	Adjusted HR (95% CI): 1.19 (0.35 to 2.96)

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; BMI = body mass index; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CHD = coronary heart disease; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; HTN = hypertension; MMSE = Mini-Mental State Examination; n = number of subjects; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; RCT = randomized controlled trial; SBP = systolic BP

Two studies[154,159] showed a statistically significant association between statin use and a reduced risk of AD (Figure 4). Some studies reported stratified analyses. There was no significant difference in the strength of association for lipophilic and hydrophilic statins,[154,157] duration of statin exposure,[154-157] or presence of APOE.[154] We used a random-effects model to compute a summary estimate of effect, which showed a significant association between statin use and decreased incidence of AD (HR 0.73; 95 percent CI 0.569 to 0.944). The forest plot, chi-square test ($Q = 5.132$, $df = 5$, $p = 0.40$), and $I^2 = 2.58$ did not suggest significant statistical heterogeneity.

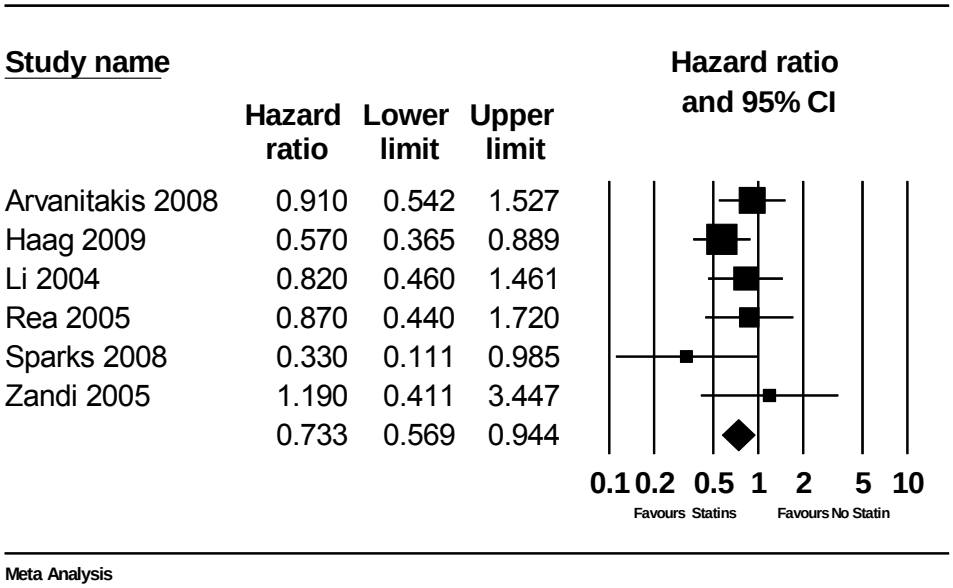

Figure 4. Meta-analysis of six cohort studies on statins and risk of developing AD. Combined estimate is given in bottom row.

Subgroup analyses grouping studies by baseline versus ongoing assessment of exposure showed no association for the two studies assessing exposure at baseline only (HR 0.958; 95 percent CI 0.602 to 1.526) and a significantly reduced risk of AD for those with a more robust assessment of exposure (HR 0.655; 95 percent CI 0.485 to 0.986). Subgroup analysis by length of followup (< 5 years versus ≥ 5 years) did not show important differences in summary effect.

A funnel plot (Figure 5) did not suggest significant publication bias.

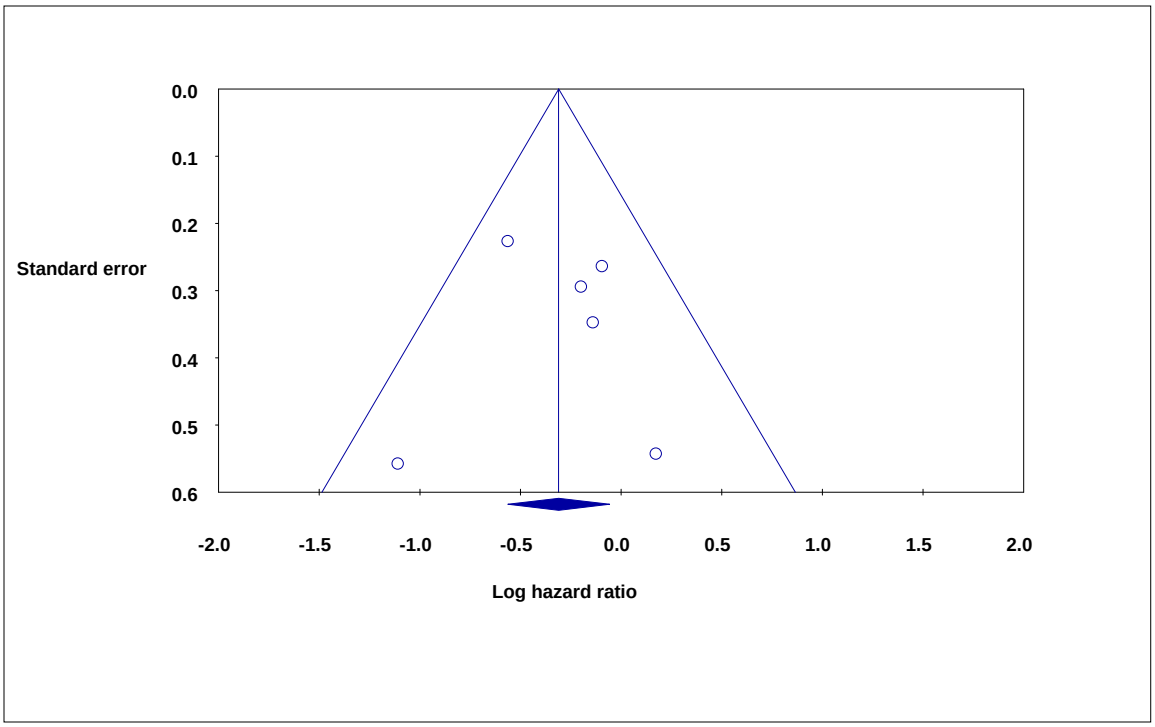

Figure 5. Funnel plot of standard error by log hazard ratio for statins and risk of developing AD

In summary, six observational studies with 4 to 17 years followup showed a moderate reduction in risk of AD with statin use.

Antihypertensives. We identified eight eligible cohort studies, described in ten publications,[99,104,107,109,160-165] that examined the use of antihypertensives and risk of incident AD (Table 22). More than 20,000 subjects and 1300 cases of incident AD were included. Five studies recruited community samples from the United States.[99,109,162-164] Two of these focus on Americans of Japanese descent.[99,163] The other studies were from Canada (Canadian Study of Health and Aging, or CSHA), the Netherlands (Rotterdam),[161,165] and Sweden (Kungsholmen).[107,160] Outcomes were measured well, although one study[107] provided few details on dementia diagnoses. Exposure information came from self-report and/or inspection of pill bottles, except in the study by Haag et al.,[165] which used pharmacy data. It is not known if as much detail was provided when a questionnaire with multiple risk factors was used, as in Lindsay et al.[104] Followup rates were between 72 and 94 percent, with the exceptions of Yasar et al.,[164] which did not report followup rates, and Peila et al.,[163] where it appears that 73 percent of normotensive subjects had missing or abnormal blood pressures and were not included in the analysis.

Four of the eight cohort studies found a decreased risk for AD with antihypertensive medications. Significant impact of antihypertensive use in the risk of incident AD was found in the Kungsholmen cohort after 3-year[160] and 6-year followup.[107] In subjects with SBP $\geq$ 140 mmHg, the RR for AD with antihypertensives was decreased (0.6; 95 percent CI 0.4 to 0.8). When both APOE e4 allele and high SBP were present, the RR for AD was 2.4 (1.4 to 4.2). This

elevated risk was mitigated when antihypertensives were used (RR 1.0; 95 percent CI 0.6 to 1.6). The Kungsholmen cohort had a mean age of 81 years at baseline, so it would be expected to have a high incidence of dementia and prevalence of hypertension (HTN). It is possible that many APOE e4 subjects would have had prevalent AD and not be eligible for inclusion in the cohort, thus selecting for individuals less susceptible to AD.

The Cache County cohort study also found an association between antihypertensive use and the development of AD.[162] When patients taking antihypertensives at baseline were followed for 3 years, the hazard ratio (HR) for incident AD was 0.64 (95 percent CI 0.41 to 0.98). This cohort was younger at inception (mean age 74.1) and was followed for a shorter time. When different classes of antihypertensives were analyzed, the result was significant only for diuretics, with an adjusted HR of 0.61 (0.37 to 0.98). When controlled for current blood pressure, statistical significance was lost, although a significant result remained when the analysis was restricted to a cohort who self-reported hypertension.

The HAAS cohort[163] was formed in mid-life and followed into later life. Compared to never-treated hypertensive subjects, antihypertensive use for > 12 years was associated with a significantly lower risk for incident AD (HR 0.35; 95 percent CI 0.16 to 0.78). Antihypertensive use for 0 to 5 years and 5 to 12 years was associated with a non-statistically significant reduced risk. There was no statistically significant difference in incident non-specific dementia between normotensive subjects (not on antihypertensives) and any hypertensive subjects treated with antihypertensives for > 12 years (HR 0.82; 95 percent CI 0.28 to 2.38). However, the confidence interval was wide and does not exclude a clinically significant difference.

Haag et al.[165] report data from the Rotterdam cohort after a mean followup of 8 years (up to 13.3 years); pharmacy records were used to determine exposure. The HR for AD per year of antihypertensive use (compared to no use) was 0.94 (95 percent CI 0.90 to 0.99). Subjects 75 years of age and younger had a statistically significant lower risk of AD when antihypertensives had been used, but subjects over 75 years did not. Use of antihypertensives for ranges of duration was significant only for use between 1.6 to5.3 years.

No association between antihypertensive use and incident AD was found in the other cohorts. The Kame[99] and CSHA cohorts[104] were followed for a mean of 6 and 5 years, respectively, at the time of these analyses. The Kame cohort[99] had a mean age at baseline of 72.6. In the CSHA cohort, the mean age at baseline was 81 for those who developed incident AD at wave 2, and 72.9 for controls. Morris et al.[109] followed a subset of the Boston EPESE study for up to 13 years. There was no clear association between HTN or use of antihypertensives and incident AD. Yasar et al.[164] used the Baltimore Longitudinal Study on Aging (BLSA) to specifically examine the impact of calcium channel blockers (CCB), both dihydropyridine (DHP), and non-DHP; neither non-specific nor specific classes of CCBs were significantly associated with incident AD over the average 13 years of followup.

In summary, data from eight cohort studies do not show a consistent association between antihypertensive use and risk of developing AD. However, most studies found a decreased risk – albeit a statistically non-significant decreased risk – with use of antihypertensive medication, suggesting a possible reduction in risk. Age of cohort group studied, length of time followed, and prevalence of HTN do not consistently explain the variability in outcomes across studies.

Table 22. Antihypertensives and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Borenstein, 2005[99] Kame Project	Community cohort (1859)	6.0 (2.7) years 90 cases AD	Self-report of antihypertensives	NINCDS-ADRDA DSM	Antihypertensive results unadjusted	34.5% of cases reported antihypertensive use versus 33.5% non-cases
Guo et al., 2001[160] AND Qiu et al., 2003[107] Kungs-holmen Project	Community cohort (1310)	5.7 years (0.1 to 8.2) 204 cases AD	Self-report and inspection of pill bottles for 2 weeks preceding baseline evaluations	DSM	Age Race Sex Educational level Baseline MMSE Vascular disease (heart disease, cardiovascular disease and diabetes mellitus) APOE genotype SBP DBP	Antihypertensive drug use with: SBP ≥ 140 mmHg: RR 0.6 (95% CI 0.4 to 0.8) DBP ≥ 70 mmHg: RR 0.6 (0.5 to 0.9) Investigators stated that "compared with those with no use of antihypertensive drugs, no APOE e4 and SBP < 140, the adjusted relative risks of AD were 3.2 (1.6-6.4) for subjects with e4 and SBP > 140 but no use of drugs, and 1.5 (0.7-3.2) for persons with e4, SBP > 140 and use of drugs" Use of antihypertensives mitigated the increased risk of the e4 and high SBP
Haag et al., 2009[165] Rotterdam Study	Community cohort (6249)	8 years (up to 13.3) 432 cases AD	Pharmacy data	NINCDS-ADRDA DSM	Age Sex DBP SBP Diabetes mellitus CVA BMI Education Smoking Total serum cholesterol Cardiovascular disease Cerebrovascular	HR (95% CI) for any use vs. no use: Per year of treatment: All subjects: 0.94 (0.90 to 0.99) Subjects ≤ 75: 0.92 (0.85 to 0.99) Subjects > 75: 0.96 (0.84 to 1.04) Duration of treatment, HR (95% CI) for AD: < 1.6 years: 0.91 (0.71 to 1.17) 1.6 to 5.3 years: 0.73 (0.55 to 0.96) > 5.3 years: 0.69 (0.46 to 1.05)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
					disease	
Khachaturian et al., 2006[162] Cache Study	Community cohort (3227)	3 years 104 cases AD	Antihypertensives, inspection of pill bottles, "current use"	NINCDS-ADRDA	Age Race Sex Number of APOE e4s History of CVA Hyperlipidemia Diabetes mellitus MI Educational level	Antihypertensive use and incident AD: HR 0.64 (95% CI 0.41 to 0.98) When restricted to subjects with self-reported HTN: HR 0.64 (0.42 to 0.96) When controlled for current SBP and DBP: HR 0.65 (0.29 to 1.42)
Lindsay et al., 2002[104] Canadian Study of Health and Aging (CSHA)	Community cohort (case-control analysis) (4088)	5 years 194 cases AD	Risk factor questionnaire (self-report)	NINCDS-ADRDA	Age Sex Education	OR for AD on antihypertensive agents: 0.91 (0.64 to 1.30) Comparison of odds ratio includes normotensive subjects
Peila et al., 2006[163] Honolulu Asia Aging Study (HAAS)	Community cohort (1251)	4 to > 12 years 65 cases AD	Self-report first three exams Pill bottle check fourth exam	NINCDS-ADRDA DSM	Age Mid-life BMI Smoking CAD CVA Atherosclerosis APOE e4 Education	Incident dementia = 108 (AD – 65; AD/VAD – 19) Duration of treatment, HR (95% CI) for AD: 0-5 years: 0.62 (0.27 to 1.43) 5-12 years: 0.54 (0.21 to1.36) > 12 years: 0.325 (0.16 to 0.78), as compared to never-treated hypertensives Untreated normotensives: 0.26 (0.10 to 0.66) Treatment > 12 years as compared with normotensives: 0.82 (0.28 to2.38) not specifically AD
Morris et	Community	2-13 years	Pill bottle inspection of all	NINCDS-ADRDA	Age	OR (95% CI) for incident AD after 4 years for

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
al., 2001[109] Boston EPESE	cohort (634)	99 cases AD	meds taken in past 2 weeks		Sex Education	antihypertensives: 0.66 (0.68 to 2.61) "No evidence of interactive effects of these medications with BP on the risk of AD"
Yasar et al., 2005[164] Baltimore Longitudi-nal Study of Aging (BLSA)	Community cohort (1092)	Average 13 years (up to 19) 115 cases AD	Self-report 1980-1990; inspection of pill bottles after 1990	NINCDS-ADRDA DSM	Sex Education Smoking BP History of heart problems	RR (95% CI) for AD with any calcium channel blocker (CCB): 0.63 (0.31 to 1.28) for a 2-year lag For DHP-CCB users vs. nonusers: 0.30 (0.07 to 1.25) for 2-year lag Non-DHP-CCB users vs. non-users: 0.82 (0.37 to 1.83) for a 2-year lag Odds for users vs. non users without regard to HTN status

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; APOE e4; epsilon 4 allele of the apolipoprotein E gene; BMI = body mass index; BP = blood pressure; CI = confidence interval; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DHP-CCB = dihydropyridine-calcium channel blockers; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; HTN = hypertension; MI = myocardial infarction; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; RR = relative risk; SBP = systolic blood pressure; VAD = vascular Alzheimer's disease

Anti-inflammatories. Our search identified one good quality systematic review examining the impact of NSAIDs on risk of developing AD.[35] This review included studies only if AD was diagnosed by validated criteria. Studies examining prevalent and incident AD and case-control studies were all included. Data on non-aspirin NSAIDs were summarized quantitatively. For our purposes, only the four cohort studies that evaluated incident AD were useful.[104,166-168]

Two studies analyzed the use of NSAIDs in community populations in the United States (Baltimore Longitudinal Study on Aging[168] and Cache County study[166]). Lindsay and colleagues[104] examined NSAID use and incident AD in the Canadian Study of Health and Aging, and In't Veld and colleagues[167] used the Rotterdam cohort. Two studies[104,168] relied on self-report of subjects regarding use of NSAIDs. Zandi and colleagues[166] used direct examination of pill bottles in addition to self-report, and In't Veld and colleagues[167] used automated pharmacy data. The latter study ran through the end of 1998 (NSAIDs were available by prescription only until 1995 in the Netherlands).

Stewart and colleagues found an RR of 0.40 (95 percent CI 0.19 to 0.84) when NSAIDs were used for more than 2 years. The Dutch study[167] reported that NSAID use at any time had an RR for incident AD of 0.86 (0.66 to 1.09), but when NSAIDs were used for more than 2 years, the RR was statistically significant at 0.20 (0.05 to 0.83). Lindsay and colleagues found a milder reduced risk with any NSAID use, reporting an OR of 0.65 (0.44 to 0.95). Finally, Zandi and colleagues reported a HR of 0.45 (0.17 to 0.97), but followup was short, only 3 years as compared to 5 to 15 years for the other studies.

The cohorts in the In't Veld and Stewart papers[167,168] were relatively young: in both cases, 78 percent of subjects were under 75 years of age at baseline. In the cohort studied by Zandi et al.,[166] the mean age was approximately 74 years, while in Lindsay et al.[104] controls had a mean age of 73 years, and subjects with incident dementia had a mean age of 81 years. The authors of this latter study also noted that 18.2 percent of their subjects died between waves of the study. In a sensitivity analysis that included decedents and estimated the probability of incident dementia in this group, there was no association between NSAID use and AD (OR 0.97; 95 percent CI 0.77 to 1.20).

These four prospective studies examining incident AD[104,166-168] included 15,990 subjects with 672 cases of incident AD. The meta-analysis of the four prospective cohort studies using a fixed-effect model showed a RR of 0.74 (95 percent CI 0.62 to 0.89). A chi-square test suggested no significant heterogeneity; $Q_3 = 1.16$; $p = 0.56$. Three of the four studies[166-168] evaluated NSAID exposure of more than 2 years. The combined RR for those three studies was 0.42 (95 percent CI 0.26 to 0.66; $Q_2 = 1.16$). An I^2 test for heterogeneity was not reported.

Our own search of the literature identified four eligible cohort studies published after the systematic review described above.[169-172] These studies are summarized in Table 23; detailed evidence tables are provided in Appendix B. All four studies had community-based populations, with a total of more than 8200 subjects. Three studies used U.S. populations and one a Swedish population. Subjects were followed for 1 to 12 years. Exposure to NSAIDs was determined by self-report and inspection of pill bottles except in the study by Breitner et al.,[172] which used a pharmacy record and self-report. Two of the papers reported that examining duration of use or a lagging time (to account both for difficulty by cognitively impaired subjects in accurately reporting exposure and for the possible lagging effects of exposure on risk) did not change the results, but the actual hazard ratios for these calculations were not included. Breitner and colleagues[172] ignored the year preceding dementia onset to avoid some of the influence of

cognitive impairment on reported NSAID use. All papers used populations with mean baseline ages in the mid 70s.

One study[171] found a reduction in risk for AD with NSAID use that was statistically significant. The same study found an association between NSAID use and reduced risk of AD in the presence of the APOE e4 allele. In their analysis, benefit was apparent only in those with at least one e4 allele. For subjects 75 or younger, the HR for AD with a history of NSAID use was 0.22 (95 percent CI 0.06 to 0.73), and for those older than 75 years, the HR was 0.45 (0.20 to 0.97). There were only three incident cases of AD in the younger group and eight in the older group. Two other studies[169,170] found no associations between NSAID use and the risk of developing AD. Breitner and colleagues[172] found an increased risk of AD in heavy users of NSAIDs, but no statistically significant effect for moderate users, using both pharmacy data and pharmacy data integrated with self-report. Analyses were adjusted for APOE status.

Table 23. NSAIDs and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Arvanitakis et al., 2008[169] Religious Orders study	Community cohort (1019)	1 to 13 years 209 incident AD	Pill bottles baseline and annually	NINCDS using CERAD	Age Sex Education Vascular risk factors APOE e4 Average of z scores	HR (95% CI) for using vs. not using at baseline: NSAIDs (not ASA): 1.19 (0.87 to 1.62) ASA: 0.84 (0.63 to 1.11) Authors reported that results were similar for cumulative use, but data were not shown
Cornelius et al., 2004[170] Kungs-holmen	Community cohort (1301)	3 to 6 years 164 AD	Self-report and bottles (script) at baseline (1987) and first followup (1991-93), not at second followup (1994-96)	DSM IIIR	Age Sex Underlying disease Educational level	RR (95% CI): NSAID only: 0.61 (0.32 to 1.15) ASA only: 1.34 (0.96 to 1.89) Either: 1.11(0.81 to1.52)
Szekely et al., 2008[171] Cardio-vascular Health Study	Community cohort (3229)	Up to 10 years 231 AD	Self-report, pill bottles, annually Analyzed as cumulative and more than or equal to 2 years or less	NINCDS	Age Sex Education APOE e4 Baseline 3MS	HR (95% CI): NSAIDs: 0.65 (0.41 to 0.88) ASA: 0.87 (0.65 to 1.16) This apparent benefit of NSAID use seemed to depend strongly on APOE status, being evident only in people with one or more e4 allele. According to results: "There was no consistent evidence of greater reduction in risk of AD with lagging of exposure, longer duration of use, or higher doses of NSAIDs," but no quantitative data were reported.
Breitner et al., 2009[172] Adult changes in Thought (ACT)	Community cohort (2736)	Up to 12 years (3-12) 356 AD	Pharmacy data and an integration of pharmacy data and self report	NINCDS DSM IV	Age Cohort Race Sex Education APOE HTN	HR (95% CI) for AD as compared to no/low use of NSAIDs: Pharmacy data alone Moderate use: 1.26 (0.97 to 1.65) Heavy use: 1.57 (1.10 to 2.23) Pharmacy + self report:

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
					Diabetes mellitus BMI Osteoarthritis Regular exercise	Moderate use: 1.15 (0.85 to 1.57) Heavy use: 1.55 (1.07 to2.24)

Abbreviations: 3MS = Modified Mini-Mental State Examination; AD = Alzheimer's disease; APOE = apolipoprotein E gene; APOE e4; epsilon 4 allele of the apolipoprotein E gene; ASA = acetylsalicylate (aspirin); BMI = body mass index; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; HTN = hypertension;; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; NSAID(s) = non-steroidal anti-inflammatory drug(s); RR = relative risk

Explanations for the disparate findings in the studies are unclear. It has been suggested that longer duration of NSAID use might be necessary to convey benefit, and that there may be a window of opportunity prior to onset of disease when NSAIDs are helpful. As noted above, it has also been suggested that the benefit from NSAIDs may be more pronounced or only present when there is an APOE e4 allele.

It is possible that studies that failed to find an association did so for different reasons. For example, it is possible the duration of followup was too brief in Cornelius et al.,[170] and that the populations in Arvanitakis et al.[169] and Breitner et al.[172] were too old. Breitner's report on the ACT cohort differs in that it uses pharmacy exposure information as well as self-report. It is not clear how much NSAID use is over-the-counter and not captured by pharmacy data. The secondary analysis by Breitner et al. included a combination of pharmacy and self-report data, but the proportions of various user groups (low, moderate, heavy) from self-report data are not reported. If APOE e4 causes an earlier onset of illness, and benefit from NSAIDs is most apparent in those with APOE e4, it would be most beneficial to follow a younger cohort to capture this effect. Additionally, those subjects with earlier onset of AD (e.g., those with APOE e4) would not have been eligible for dementia-free inception cohorts forming later in life. The most strikingly positive findings involved longer duration of use in relatively younger cohorts.[167,168]

A random-effects meta-analysis combining the cohort studies in the systematic review by Szekely et al.[35] and the more recent studies summarized above is shown in Figure 6. Studies were significantly heterogeneous ($Q = 40.84$, $df = 7$, $p < 0.001$, $I^2 = 83$ percent). Any use of NSAIDs was not associated with the risk of AD (RR 0.83; 95 percent CI 0.63 to 1.09). Analyses examining the effect of duration and level of exposure did not explain the heterogeneity. A sensitivity analysis removing one study at a time found that when the study by Breitner et al. was removed, the summary estimate shows an association between NSAID use and lowered risk for incident AD (HR 0.79; 95 percent CI 0.69 to 0.91). It is unclear why this study is an outlier.

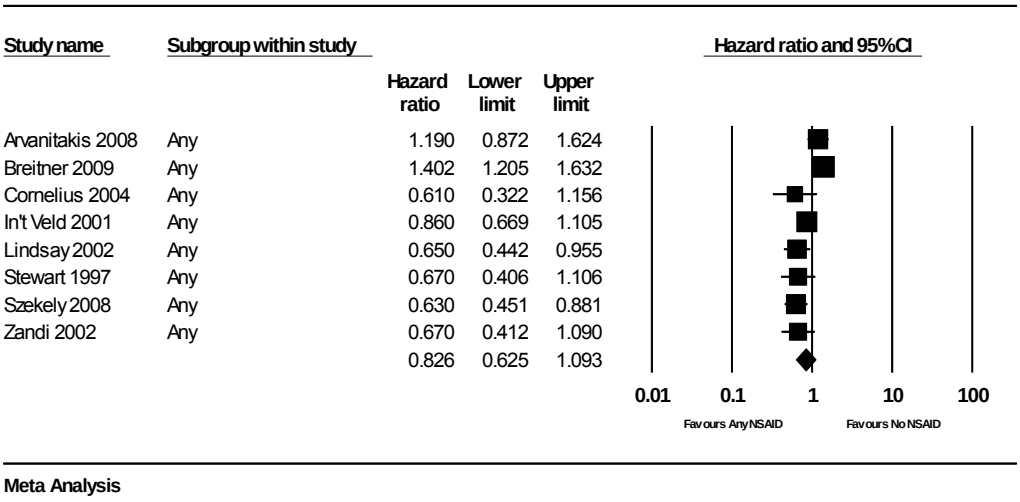

Figure 6. Meta-analysis of eight cohort studies on NSAIDs and risk of developing AD. Combined estimate is given in bottom row.

In summary, these prospective cohort studies do not provide clear consensus on the impact of NSAIDs in the reduction of risk for AD. Any use is associated with a moderate statistically significant decreased risk, but studies are heterogeneous. Variability may be explained by interactions with genetic predispositions, duration of use of NSAIDs, and possibly even a therapeutic window of benefit.

Gonadal steroids. We identified one good quality systematic review that examined the association between gonadal steroids and the development of AD.[38] Cohort studies were reviewed for the effects of hormone replacement therapy (HRT) on cognitive decline and dementia risk. Selected studies had sufficient data to calculate an odds ratio for risk of AD or AD-like dementia, had a control group for comparison, and made a clinical diagnosis of AD. The review included 2 cohort studies (1596 subjects) and 10 case-control studies; 10 were from the United States, 1 from European countries, and 1 from Australia. Subjects in the two cohort studies had had an average age of 61.5 years in one study and 74.2 years in the other. Study quality for cohort designs was fair; one study had limitations because it did not maintain comparable groups and did not report loss to followup. The other cohort study was limited because it did not assemble comparable groups at baseline. Length of followup and level of covariate adjustment ranged from 1 to 16 years, and results were adjusted for education, age, and ethnicity. The formulation of estrogen varied, with most participants using oral conjugated equine estrogen (CEE), though some subjects used other oral estrogens or estrogen delivered using a transdermal delivery system. The duration of estrogen use was not stated in one cohort study and ranged in duration from 2 months to 49 years (average 6.8 years) in the other. The cohort studies diagnosed AD using structured criteria such as NINCDS-ADRDA.

Studies were combined using a random-effects model. A test for heterogeneity suggested that the studies were not heterogeneous ($p > 0.1$). No I^2 was reported. A funnel plot that included all 12 studies suggested possible publication bias. In the two cohort studies, estrogen use was associated with a statistically significant decreased risk of AD (RR 0.50; 95 percent CI 0.30 to 0.80).

The review authors conducted stratified analyses for cohort versus case-control study designs; results are summarized in Table 24.

Table 24. Gonadal steroids and risk of developing AD – results from stratified analyses by LeBlanc et al., 2001[38]

Studies analyzed	RR (95% CI)
Cohort studies (n = 2) Case-control studies (n = 10)	0.50 (0.30 to 0.80) 0.71 (0.56 to 0.91)
Results from 2 cohort studies and 2 case control studies (excluding 8 poor quality case-control studies)	0.64 (0.32 to 1.06)
Results excluding 3 case-control studies with proxy bias	0.72 (0.55 to 0.96)

Abbreviations: CI= confidence interval; RR = relative risk

Summary RRs were similar for studies with NINDS-ADRDA diagnosed AD and those using other, less strict AD diagnostic criteria. Exclusion of a study with uncertain confidence intervals and a study with low SE (high weight) did not significantly change the risk assessment.

The authors of the meta-analysis concluded that hormone replacement therapy decreased risk of dementia, but most studies had important methodological limitations. The effect of hormones

on dementia may be over-estimated if participants with memory problems or proxy respondents for women with dementia did not remember or were not aware of HRT exposure. Further limitations included a wide range of different estrogens, presence or absence of progestins, timing of estrogen treatment (perimenopausal versus early or late post-menopausal), and duration of use.

Our search did not identify any new observational studies published since 2001. See the section on "Gonadal Steroids" under Question 3 for results of RCTs examining the therapeutic and adverse effects of gonadal steroids used to delay the onset of AD.

Cholinesterase inhibitors. We did not identify any systematic reviews or primary studies in cognitively normal samples that evaluated the association between cholinesterase inhibitors and incident AD.

Memantine. We did not identify any systematic reviews or primary studies that evaluated the association between memantine and incident AD.

Social, Economic, and Behavioral Factors

Early childhood factors. We did not identify any systematic reviews that examined the association between childhood exposures and development of AD. We identified one eligible cohort study.[173] The study is summarized in Table 25; a detailed evidence table is provided in Appendix B. The study was drawn from U.S. communities, but some of the participants lived in religious order facilities. The length of followup averaged 5.6 years. At baseline, participants were not demented. Self-reported information on variables related to childhood socioeconomic status was collected when the participants were an average of 75 years old. This information was then used to derive indices of socioeconomic status. There was no objective validation of the derived indices. The sample selection method only partially minimized selection bias because as part of the enrollment criteria participants were required to agree to post-mortem autopsy, which may have resulted in some selection bias. The study did not report comparison of baseline characteristics between those exposed and unexposed. Standard criteria were used for the diagnosis of AD, but the study did not use an informant report as part of the diagnostic process. The authors did not report whether the diagnosis was blind to exposure status; however, it is unlikely that details like those used as part of this childhood socioeconomic index would be discussed during the diagnostic process. Analyses were appropriate and controlled for relevant potential confounders. This study showed that neither early-life household nor community socioeconomic factors influenced risk of incident AD in later life. In conclusion, there is no evidence supporting an association between these early childhood factors and AD, but there is also not sufficient evidence to rule out a possible association.

Table 25. Childhood socioeconomic status and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results)
Wilson et al., 2005[173]	Community cohort (some lived in religious order facilities) (859)	5.6 years (mean) 154 AD cases	Self-report and county public records Information collected by self-report: (1) parental education, (2) paternal occupation, (3) number of children in the family, and (4) participant's education level. Information collected from public records for the participant's county of birth: (1) literacy rate, (2) percent of children in county attending school, and (3) the Duncan socioeconomic index for head of households for the county.	NINCDS-ADRDA	Age Sex Education Socioeconomic status indicators	For a 1-unit increase in socioeconomic status indicator: Childhood household socioeconomic status: HR 1.12 (95% CI 0.88 to 1.42) Community socioeconomic status: HR 1.35 (95% CI 0.93 to 1.96)

Abbreviations: AD = Alzheimer's disease; CI = confidence interval; HR = hazard ratio; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association

Education/occupation. Because of their close association, education and occupation are considered together here.

Education. Our review of studies examining the association between years of education and AD focused on those studies in which assessing this association was the main aim of the study. Reviewing all studies, such as those primarily focused on estimating incidence rates of AD and assessing numerous factors that predict AD, was beyond the scope of this review.

We identified one good quality systematic review that examined the association between years of education and development of AD.[49] The review included nine prospective cohort studies.[118,174-181] It also included six case-control studies; however, given the numerous weaknesses of case-control studies in assessing risk factors, the current summary describes only the cohort studies. The nine cohorts included 22,726 subjects; four studies were from the United States, four from European countries, and one from Japan. Studies were selected that used clear diagnostic criteria for dementia and AD, provided information about years or level of education of participants, controlled for potential confounders, and provided odds ratios or relative risks or sufficient data to calculate these figures.

There was not a structured quality assessment of the studies reported in this systematic review; however the strict inclusion/exclusion criteria provided an indirect assessment of quality, and the study characteristics for key design variables were reported. Length of followup was not reported. However, all studies included in the review reported on incident AD, and education is typically completed in early adulthood, meaning that exposure most likely occurred years prior to participation in the study. There was no information provided on the followup rates in the studies. The covariate adjustment for most studies included at least age and sex; some studies included additional covariates such as occupation, APOE, ethnic group, leisure activities, and health conditions. Exposure was determined by self-report and categorized as high, medium, or low levels of education. The definition of these three levels of education appeared to differ across studies. All studies used DSM and NINDS-ADRDA criteria for diagnosis of AD and dementia.

Studies were combined using both fixed-effect and random-effects models to calculate pooled relative risks. When results from the two approaches differed, only the random-effects models were reported, as they represent more conservative estimates. Heterogeneity was tested by using the Cochrane Q statistic, and the Ri statistic. Publication bias was assessed graphically using a funnel plot. To assess the potential effect of publication bias on the pooled relative risk, the authors conducted sensitivity analysis using three assumptions: (1) published studies included only half of all studies conducted; (2) the unpublished studies found null associations; and (3) the unpublished studies included as many cases and controls as the average of the published studies.

To briefly summarize the main findings, fewer years of education were associated with a greater risk of AD compared to individuals with the highest level of education (Table 26). Analyses were not conducted to allow for assessment of a dose-response association. However, when the lowest and medium level education groups were combined, the relative risk decreased compared to the findings from the analysis using just the lowest level education group. This might be interpreted as an indirect measure of a dose-response effect. Both the funnel plot and the sensitivity analyses assessing extreme assumptions concerning unpublished studies showed that the findings were robust and that no publication bias was evident. The authors concluded that having fewer years of education is associated with greater risk of AD.

Table 26. Education and risk of developing AD – results from studies reviewed by Caamano-Isorna et al., 2006[49]

Comparison	RR (95% CI)	Ri* (p value)[+]
Lowest education level versus highest AD (n = 9 studies)	1.59 (1.35 to 1.86)	0.33 (0.157)
Any education level other than highest versus highest AD (n =5 studies)	1.32 (1.09 to 1.59)	0.61 (0.055)

* Ri – proportion of the total variance due to between-study variance. Large values (> 0.75) indicate large heterogeneity between studies; small values (< 0.4) indicate lack of heterogeneity.
[+] Cochrane Q statistic.
Abbreviations: AD = Alzheimer's disease; CI = confidence interval; RR = relative risk

We identified two additional eligible cohort studies published since 2004 examining risk of AD in relation to years of education completed.[182,183] These two studies are summarized in Table 27; detailed evidence tables are provided in Appendix B. One study used a community sample,[182] and one used a religious order sample in the United States.[183] In the study by Ngandu and colleagues,[182] participants were non-demented at baseline. In the study by Tyas and colleagues,[183] participants were either cognitively normal or had MCI at baseline. Length of followup ranged from 1 to 21 years. Exposure was determined based on self-reported information about years of education completed; this is a standard and well-accepted method of data collection for this information. The studies used sample selection methods to minimize selection bias; however, one study required that participants agree to brain donation at the time of death, and this may have introduced some selectivity into the sample.[183] One study specifically stated that they used standard criteria for the diagnosis of AD;[182] the other study did not.[183] Neither study used an informant report as part of the diagnostic process. The study that did not state specific standard criteria did describe criteria that appeared to be in keeping with DSM criteria.[183] However, while this approach may provide a diagnosis of dementia, it is not clear that it would provide a reliable differential diagnosis of AD. It was not reported whether the dementia diagnosis was assigned blind to the exposure level, but it seems likely that those assigning the diagnosis were aware of the participant's level of education. However, because the association between education and AD was not the primary outcome for these studies, this knowledge may not have biased the results. Analyses were appropriate and controlled for relevant potential confounders.

Both studies reported an inverse association between years of education and risk of AD (Table 27). In conclusion, the preponderance of evidence indicates that more years of education may provide protection from AD. It is not clear whether education is a surrogate for other factors such as occupation, baseline intelligence, or socioeconomic status. It is also not clear whether more years of education actually prevents AD, delays onset of the disease, or just delays the detection of the cognitive decline. Two of the cohort studies included in the systematic review discussed above address some of these points. Karp and colleagues[174] reported that both low education and low socioeconomic status increase risk of AD, but only low education remains a significant predictor when both factors are simultaneously included in the model. Stern and colleagues[176] found that either low education or a low-level occupation increased risk of AD, but those with both low education and low occupation had the greatest risk. Combined, these

findings suggest that education contributes to risk of AD independently of occupation and other socioeconomic factors.

Table 27. Years of education and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Ngandu, et al., 2007[182]	Community cohort (2000)	Mean 21 years (4.9) Number or AD cases NR	Self-reported education	NINCDS-ADRDA DSM	Age Sex Followup time Community of residence SES variables Vascular and lifestyle characteristics APOE Late-life diseases and depressive symptoms	Education associated with risk of dementia in a dose-dependent manner Unadjusted ORs (95% CI) for AD: Education ≤ 5 years = reference 6 to 8 years of education: OR 0.49 (0.24 to 1.00) ≥9 years of education: OR 0.15 (0.05 to 0.40) None of the covariates were significant in the models, so the effect of education appears to be independent predictor of AD
Tyas et al., 2007[183]	Community cohort (members of a religious order)	1 to 11 years Number or AD cases NR	Self-reported education	Not specifically stated, but appears to basically be consistent with DSM	Age APOE Prior cognitive state	OR (95% CI) with age, education and APOE in the model and graduate school as the reference: Transition from intact cognition to dementia: ≤ High school: 41.48 (4.0 to 42.4) Undergraduate degree: 2.07 (0.28 to 15.1) Transition from MCI to dementia: ≤ High school: 1.11 (0.49 to 2.53) Undergraduate degree: 0.76 (0.45 to 1.29)

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; NR = not reported; OR = odds ratio; RR = relative risk; SES = socioeconomic status

Occupation. We identified five eligible cohort studies examining risk of AD in relation to occupation.[174,176,184-186] The studies are summarized in Table 28; detailed evidence tables are provided in Appendix B. Two of the studies used community samples in the United States,[176,184] and three used community samples in Europe.[174,185,186] Two of these studies were based on the same sample,[174,186] but they used different lengths of followup and different, but related, predictor variables. Length of followup ranged from 1 to 6.4 years. Exposure was determined based on self-reported information about occupation. The studies used sample selection methods to minimize selection bias. All studies stated that they used standard criteria for the diagnosis of AD, but only one of the studies used an informant report as part of the diagnostic process.[185] It was not reported whether the dementia diagnosis was assigned blind to the exposure level, but it seems likely that those assigning the diagnosis were aware of the participant's occupation. However, because the association between occupation and AD was not the primary outcome for the parent studies of these substudies, this knowledge may not have biased the results. Analyses were appropriate and controlled for relevant potential confounders. The studies used different scales to categorize occupational characteristics, making it difficult to make direct comparisons.

Overall, the findings suggest that typically the relatively modest associations between occupation and incident AD become statistically non-significant once years of education are included in the model. However, one study did report that low occupation level combined with low education further increased the risk of AD, in addition to the effect noted for low education alone.[176] These results point to the complex inter-relationships among education, occupation, and other markers of socioeconomic status.

In conclusion, the studies to date do not support an association between occupational level and risk of AD that is independent of the influence of education level.

Table 28. Occupation and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Evans, et al., 1997[184]	Community cohort (642 analytical sample)	4.3 years 95 AD cases	Self-reported occupation coded according to level of prestige. Self-reported income and education	NINDCS-ADRDA	Age Sex Followup interval	OR (95% CI): Lower occupation prestige (0.96; 0.93 to 0.99) but not lower income (0.80; 0.63 to 1.02) was associated with increased risk of AD when individually assessed When education (0.85; 0.75 to 0.95), occupational prestige (0.98; 0.94 to 1.01) and income (0.92; 0.69 to 1.22) were simultaneously entered into the model, only education remained significant
Karp, et al., 2004[174]	Community cohort (931)	3 years 76 AD	Self-reported occupation and education. Lifetime SES estimated based on occupation. Socioeconomic mobility based on occupation changes	NINCDS-ADRDA DSM	Age Sex Vascular disease Alcohol use	RR (95% CI): Lifetime low SES alone in model: 1.6; 1.0 to 2.5 Combined model: Low education: 3.3; 1.8 to 6.1 Low SES: 1.0; 0.6 to 1.6 Main finding: Low education and low SES are individually associated with increased risk of AD, but only low education remains a risk factor when both factors are examined simultaneously.
Stern, et al., 1994[176]	Community cohort (593)	1 to 4 years 106 dementia cases, of which 97 were AD	Self-reported education and occupation Occupation dichotomized as: High (manager/ business/ government, professional /technical)	NINCDS-ADRDA DSM	Age Sex	RR (95% CI) for dementia: ≥ 8 years of education = reference < 8 years of education: 2.02 (1.33 to 3.06) High occupation = reference Low occupation: 2.25 (1.32 to 3.84) High education and high occupation = reference

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
			versus Low (unskilled/ semi-skilled, skilled trade or craft, clerical/office worker			Low education and low occupation: 2.87(1.32 to 3.84)
Helmer, et al., 2001[185]	Community cohort (2950)	Mean 6.4 years 251 AD cases	Self-reported occupation Occupation categorized as: professional/ managerial (reference), housewives/ inactive, farmers, domestic service employees, blue collar workers, craftsmen/ shopkeepers	NINCDS-ADRDA DSM	Age Sex Educational level Tobacco use Alcohol use Vascular factors Income	Overall, there was no association between occupation and incident AD. Risk of AD seemed to be associated with occupation differently by sex: being a craftsman and shopkeeper was associated with a protective risk among women (RR 0.44; 95% CI: 0.23 to 0.87), whereas the risk was increased among men (RR 2.05; 1.02 to 4.11).
Qiu, et al., 2003[186]	Community cohort (913)	6 years 197 AD	Self-reported occupation Categorized as: 1) Manual a) Skilled vs. unskilled b) Service production vs. goods production 2) Non-manual	DSM	Sex Educational level (< 8 years vs. ≥ 8 years) Baseline cognitive status Vascular disease (heart disease, CVD, DM)	Compared with non-manual work, manual work was not significantly associated with an increased risk of AD: RR 1.2 (95% CI 0.9 to 1.7) Compared with non-manual work, manual work involving goods production had a multi-adjusted RR of 1.6 (95% CI 1.0 to 2.5; p = 0.046) for AD

Abbreviations: AD = Alzheimer's disease; CI = confidence interval; CVD = cardiovascular disease; DM = diabetes mellitus; DSM = Diagnostic and Statistical Manual of Mental Disorders; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; RR = relative risk; SES = socioeconomic status

Social engagement. We did not identify any good quality systematic reviews that examined the association between social engagement and development of AD. We identified five relevant and eligible cohort studies.[187-191] These studies are summarized in Table 29; detailed evidence tables are provided in Appendix B.

Social engagement as a risk factor was defined by different exposures in the studies, including objective measures such as marital status, living situation, number of people in social network, as well as subjective measures such as feelings of loneliness and perceptions of social support. Although five social engagement studies were identified, the measurement of exposure and reporting of outcomes varied among the studies. Hence, results were not combined to provide a single summary statistic; rather, qualitative descriptions of the studies are provided in what follows.

Two of the studies drew their sample from the United States;[188,191] the other three were from Europe.[187,189,190] All studies chose community samples and enrolled non-demented participants. The length of followup ranged from 3.3 to 21 years. Wilson et al.[188] considered loneliness as a risk factor and measured this using a modified version of the de Jong Gierveld Scale with a 5-point scoring system. It included statements such as "I miss having people around" and "I often feel abandoned." In the same study, social isolation was inferred from two indicators of social functioning, social network size and frequency of participating in social activity. Fratiglioni et al. measured social network, taking into account martial status, whether subjects lived alone or not, and contact with friends and family, including satisfaction with social contact.[189] In the study by Saczynski et al., social engagement consisted of marital status; living arrangement; participation in social, political, or community groups; participation in social events with coworkers; and the existence of a confidant relationship.[191] The other two studies[187,190] defined social engagement based on marital status.

None of the studies had objective validation of exposure. Two studies used informant interviews, one of them to confirm exposure data,[191] and the other only when the participant was unable to answer questions.[189] Only two studies examined baseline characteristics by exposure.[190,191] No information on blinding of the diagnostic assessment to exposure status was provided in any of the studies. Although information about social activities is not a routine part of dementia assessment, marital status is commonly asked about in many assessments.

Of the studies that examined marital status and AD, one study found that those who were never married had a higher risk of AD (RR 2.31; 95 percent CI 1.14 to 4.68).[187] In this study, being widowed or divorced was not associated with AD. Fratiglioni et al. found that being single and living alone was associated with an increased risk of AD (RR 1.9; 95 percent CI 1.2 to 3.1), but being widowed, divorced, or married but living alone did not significantly increase risk of AD.[189] Hakansson et al. also found that those who were without a partner *after* midlife had an increased risk of AD (OR 5.0; 95 percent CI 1.4 to 17.5). The association between being without a partner *at* midlife and risk of AD was not statistically significant. (OR 2.06; 95 percent CI 0.9 to 4.7).[190] Wilson and colleagues found that a person with a high degree of loneliness (score 3.2, 90th percentile) was about 2.1 times more likely to develop dementia during followup when compared with a person with a low degree of loneliness (score 1.4, 10th percentile).[188] In the same study, the risk of AD associated with loneliness decreased (RR 1.41; 95 percent CI 0.97 to2.06) after adjusting for a 9-item CES-D score (after removing one item about loneliness), whereas the risk of AD associated with the CES-D score was decreased by half after controlling for loneliness. In the studies that looked at social network and engagement, poor or limited social networks were associated with a higher risk of incident dementia (RR 1.87; 95 percent CI 1.12 to 2.1), and

participants who were not satisfied with social contact with children were also at a higher risk (RR 2.0; 95 percent CI 1.2 to 3.4).[189] Though social engagement at midlife was not significantly associated with AD, a decline in social engagement from mid- to late life was associated with an increased risk of AD (HR 1.87; 95 percent CI 1.12 to 3.13).[191]

In conclusion, across three studies[187,189,190] there was a consistent association between an increased risk of AD and being single and not cohabiting with a partner in later life. Generally, this association was not present for individuals who were divorced or widowed. But one exception to this is a reported association for increased risk of AD among individuals who were widowed both at midlife and later life (OR 7.67; 95 percent CI 1.67 to 40.0) compared to those who were cohabiting at both time points.[190] Further analyses of subgroups based on APOE genotype showed that this association was due primarily to those with at least one APOE e4 allele (OR 25.55; 95 percent CI 5.7 to114.5; $P < 0.001$) when compared to APOE e4 non-carriers who were cohabiting at both time points.[190] Some caution in drawing conclusions from these results is warranted given the wide confidence intervals. Further studies are needed to confirm these findings regarding cohabitation, marriage and AD.

There is also preliminary evidence that a higher degree of loneliness, dissatisfaction with social contacts, and decreased social networks might also be risk factors for AD. As a change from high to low social engagement from mid- to late life was associated with a higher risk of AD compared to consistently low or consistently high social engagement, it is possible that the decrease in social engagement may be associated with changes due to early AD. Further studies are needed to clarify the direction of the relationship between social engagement and AD.

Table 29. Social engagement and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Helmer et al., 1999[187] PAQUID	Community cohort (5554 in cohort; 3777 [68%] agreed to participate)	4.3 years (SD 1.4) 190 incident cases of dementia, 140 of which were AD and 50 "other"	Marital status assessed by self-report: 1) Married or cohabitant (n = 2106) 2) Never married (n = 179) 3) Widowed (n = 1287) 4) Divorced or separated (n = 103) 215 initially married but widowed during followup considered married until the death of spouse, then considered widowed	NINCDS-ADRDA	Number of people in the social network Satisfaction with work Living alone Number of leisure activities Baseline CES-D Education Wine consumption Sex Age	RR (with 95% CI): Married (reference; n = 44) Widowed (n = 74): RR 0.82 (0.46 to 1.44); p = 0.487 Never married (n = 18): RR 2.31 (1.14 to 4.68); p = 0.02 Divorced (n = 4); RR 0.93 (0.26 to 3.31); p = 0.917
Wilson et al., 2007[188] Rush Memory Aging Project	Community cohort (1023; 857 after exclusions)	Mean 3.3 years Range 2 to 5 years 76 AD cases	1) Loneliness: Self-report (questionnaire) 2) Social isolation: Self-report	NINCDS-ADRDA	Age Sex Level of educational achievement Social network Social activity	Risk of clinical AD increased by approximately 51% for each point on the loneliness scale (RR 1.51; 95% CI 1.06 to 2.14) Relation of loneliness to AD incidence after controlling for social network and social activity in the above model: RR 1.45; 95% CI 1.01 to 2.09
Saczynski et al., 2006[191]	Community cohort (3508)	Mean 27.5 years for midlife social measures and 4.6 years for late life	Social engagement – assessed using a composite score of the following: 1) Marital status; 2) Living	NINCDS-ADRDA DSM	Age Education Cognitive Abilities Screening Instrument score,	Midlife social engagement not associated with incident dementia Compared to highest social engagement in late life, lowest social engagement had a higher risk of developing dementia (HR 2.34;

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
			arrangement; 3) Participation in social, political, or community groups; 4) Participation in 5) social events with coworkers; 6) Existence of a confidant relationship		APOE e4 allele status History of stroke, coronary heart disease, depression, or disability	95% CI 1.18 to 4.65) Compared to consistently high social engagement in mid- and late life, those whose social engagement decreased from mid- to late life had a higher risk of incident dementia (HR 1.87; 95% CI 1.12 to 3.13)
Fratiglioni et al., 2000[189]	Community cohort (1473)	3 years	Social network 1) Marital status; 2) Living arrangement; 3) Contact with children; 4) Satisfaction with contacts; 5) Close social ties	DSM	Age Sex Educational level Baseline cognitive status Physical function (ADLs) Depression Vascular disease	Compared to extensive or moderate social network, those with a poor or limited social network were at increased risk of developing dementia (RR 1.6; 95% CI 1.2 to 2.1) Compared to daily to weekly contact with children and satisfied with this contact, those who were not satisfied also had a higher risk of developing dementia (RR 2.0 (1.2 to 3.4) Relative risk of developing dementia compared with married and living with someone (RR [95% CI]): Single and living alone 1.9 (1.2 to 3.1) Married and living alone 1.5 (0.4 to 6.4)
Hakansson et al., 2009[190]	Community cohort (1449)	Average 21 years	Marital status (married/co-habiting, single or divorced)	MMSE and NINCDS-ARDA	Age Sex Educational level Baseline cognitive status BMI APOE Systolic BP	Risk of AD (44/1216): By status at midlife (OR [95% CI]): Without partner: 2.06 (0.9 to 4.7) Widowed: 2.52 (0.8 to 7.7) Single/divorced: 1.78 (0.7 to 4.9) By status in late-life (OR [95% CI]):

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
					Region of residence Smoking Occupation Physical activity at work Depression at midlife	Widowed or divorced after midlife: 5.0 (1.4 to 17.5)

Abbreviations: AD = Alzheimer's disease; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; RR = relative risk; SD = standard deviation

Cognitive engagement. For the purposes of this review, we have categorized leisure activities into three categories: (1) cognitively engaging activities (e.g., puzzles, reading, and board or card games); (2) physical activities; and (3) other leisure activities that do not fall into the first two categories (e.g., membership in organizations such as clubs). The first group (cognitively engaging activities) also includes cognitive training RCTs. We have attempted to group the results from studies into these three categories, however, in cases in which studies grouped activities together from more than one category, we have assigned the studies to one of these categories based on the characteristics of the majority of items in the grouping. We begin with cognitively engaging activities, then proceed to physical activities and other leisure activities.

We did not identify any good quality systematic reviews that examined the association between cognitive engagement and development of AD. We identified four eligible cohort studies.[192-195] These are summarized in Table 30; detailed evidence tables are provided in Appendix B. Three studies drew samples from U.S. communities;[192-194] and one study used a community sample in Europe.[195] In all four studies, participants were non-demented at baseline. Length of followup across the studies was approximately 3.0 to 5.0 years (mean, median, or time span for mean number of annual assessments). All four studies used self-report of the frequency of involvement in specific activities, but three of the studies asked exclusively about current involvement in activities,[192,194,195] while the fourth inquired about involvement in activities across the lifespan.[193] There was no objective validation of this method, but one of the studies[194] did ask an informant to confirm the participant's report of involvement in activities. One study used sample selection methods that minimized selection bias,[195] while the other three studies used methods that partially minimized selection bias. One study compared baseline characteristics by exposure status.[195] All four studies used standard criteria for the diagnosis of AD, but only one used an informant report as part of the diagnostic process.[194] None of the studies noted whether the diagnosis was blind to exposure status; however, it is unlikely that details of involvement in these types of activities would be discussed during the diagnostic process. Analyses were generally appropriate and controlled for relevant potential confounders.

All four studies showed a decreased risk of AD associated with more frequent involvement in activities considered to be cognitively engaging. One study assessed the influence of APOE on the association between current cognitive activity and AD and reported that APOE e4 status did not change the risk estimate, and that there was no interaction between cognitive activity and the APOE e4 allele.[192] Another study[193] reported that the frequency of past cognitive activity also was associated with risk of AD (RR 0.56; 95 percent CI 0.36 to 0.88). However, when current and past activity were assessed in the same model, the effect of past activity was eliminated (HR 0.80; 95 percent CI 0.49 to 1.30), but the effect of current activity remained substantially unchanged (HR 0.47; 95 percent CI 0.34 to 0.66). Cognitive, physical, and social activity levels are often correlated. One study conducted analyses using physical and social activity levels as covariates to assess their influence on the association between cognitive activity and incident AD and found that the results remained unchanged.[193] A reduction in cognitive activities may occur in the context of mild cognitive impairment as one of the early symptoms of prodromal AD. One study conducted sensitivity analyses, successively excluding individuals with low baseline MMSE, incident dementia within first 2 years of followup, and then prevalent MCI, to assess whether the association between increased cognitive activity and incident AD may be attributed solely to individuals with potential prodromal AD.[195] The hazard ratios for these analyses

remained similar to those for the full sample, but some of the confidence intervals included 1.0 which may reflect the reduced sample size.

In conclusion, the available evidence supports an association between increased involvement in cognitive activities and decreased risk of AD. The one study that assessed past and current participation in cognitive activities found that current activities explained the protective association. Further work is needed to confirm the finding[195] that the reduced involvement in cognitively stimulating activities among those who develop AD does not reflect early symptoms of the disease given the long sub-clinical prodromal period for AD. Validation of both the type and level of exposure is needed.

Table 30. Cognitive activities and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Wilson et al., 2002[192]	Community cohort (some lived in religious order facilities) (733)	4.5 years (mean) (AD cases developed dementia after a mean followup of 3.0 years) 111 AD cases	Self-report of frequency of current involvement in the following activities: viewing television; listening to radio; reading newspapers; reading magazines; reading books; playing games such as cards, checkers, crosswords, or other puzzles; and going to museums	NINCDS-ADRDA	Age Sex Education APOE Depression Medical conditions	Adjusted HR per 1-point increase on a 5-point cognitive activity scale score: 0.67 (95% CI 0.49 to 0.92)
Verghese et al., 2003[194]	Community cohort (469)	Median 5.1 years 61 AD cases 124 dementia cases	Self-report of frequency of current involvement in the following activities: reading books or newspapers, writing for pleasure, doing crossword puzzles, playing board games or cards, participating in organized group discussions, and playing musical instruments	NINCDS-ADRDA DSM	Age Sex Educational level Medical illness Baseline Blessed test score Participation in other leisure activities	Adjusted HR: Higher cognitive activity level: 0.93 (0.88 to 0.98) Individual cognitive activities associated with decreased risk of dementia: Reading: HR 0.65 (0.43 to 0.97) Playing board games: HR 0.26 (0.17 to 0.57) Playing musical instruments: HR 0.31 (0.11 to 0.90)
Wilson et al., 2007[193]	Community cohort (residents of continuous care retirement communities and subsidized housing facilities) (829)	Mean of 3.2 annual followup assessments 90 AD cases	Self-report of frequency of cognitive activities across the lifespan. Activities included activities such as reading a newspaper, playing games like chess or checkers, visiting a library, or attending a play	NINCDS-ADRDA	Age Sex Educational level	Adjusted HR: Higher current cognitive activity level: 0.58 (0.44 to 0.77)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Akbaraly et al., 2009[195]	Community cohort (5692)	4 years 105 AD cases	Self-report of monthly frequency of doing crosswords, playing cards, attending organizations, going to cinema/theater, and practicing an artistic activity	NINCDS-ADRDA DSM	Age Sex Study center (Dijon or Montpelier) Marital status Educational level Occupational grade Vascular risk factors: - Diabetes - HTN - High cholesterol - History of vascular disease Depressive symptoms (CES-D > 16) Physical function (instrumental ADL score > 0) Cognitive impairment (MMSE score < 24) APOE genotype	HR (95% CI) for stimulating leisure activities and AD with lowest tertile as reference: High: 0.39 (0.21 to 0.71) Mild: 0.45 (0.26 to 0.77) In a sensitivity analysis excluding those with low MMSE at baseline, then those with incident AD at 1st followup, then those with MCI at baseline, the HR for stimulating leisure activities and lower risk of AD remained similar to results from entire sample, but some of the confidence intervals included 1.0.

Abbreviations: AD = Alzheimer's disease; ADL = activities of daily living; APOE = apolipoprotein E gene; CI = confidence interval; CES-D = Center for Epidemiologic Studies Depression scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; HTN = hypertension; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association

Physical activities. We did not identify any good quality systematic reviews that examined the association between physical activity and development of AD. We identified 12 eligible cohort studies.[85,118,194-202,203] These studies are summarized in Table 31; detailed evidence tables are provided in Appendix B. Five studies used samples from U.S. communities,[85,194,197,198,202] five from communities in Europe,[195,196,200,201,203] one from Canada,[199] and one from Japan.[118] Of these, one study used a sample from a health maintenance organization,[198] one used a sample of twins,[196] one used a community sample but also included institutionalized individuals,[203] and the remainder of the studies used community samples. Two of the studies used a sample from the same parent study where one of the reports focused on leisure time physical activities and the other reported on work-related physical activities.[200,201] At baseline, participants were cognitively normal in three studies,[196,199,203] non-demented in seven studies,[85,118,194,195,197,198,202] and are assumed here to have been non-demented in the other two studies based on the mean baseline age of the sample.[200,201] Length of followup across the studies was approximately 3.9 to 31 years. All studies used self-reported information on involvement in physical activities; some asked about specific activities, and others asked more general questions about any physical activities (information collected in each study is detailed in Table 31). There was a fair degree of overlap among the activities across those studies that asked about specific activities and provided this detailed information in the article. Most studies asked about current physical activities (at the time of the interview), but one study asked about activities during the previous 25 years (from age 25-50).[196] The span of years for followup reflects that some studies collected information about mid-adult life physical activities, while others collected information about later life physical activities. One study averaged the reported physical activity level in mid- and late-life.[202] In general, there was no objective validation of the accuracy of this self-reported exposure to physical activity. However, one study examined construct validity by comparing the combined physical activity score with reported markers of health hypothesized to be related to exercise and self-rated health.[197] Ten of the studies used sample selection methods to minimize selection bias, one partially used such methods,[194] and for one study it was not possible to determine whether the sample selection methods minimized selection bias.[118] Eight studies compared some baseline characteristics by level of physical activity.[85,195-198,200-202] The other studies did not compare baseline characteristics between those exposed and unexposed. All studies used standard criteria for the diagnosis of AD, but only three of the studies used an informant report as part of the diagnostic process.[196,197,203] None of the studies noted whether the diagnosis was blind to exposure status; however, it is unlikely that details of involvement in these types of activities would be discussed during the diagnostic process. Analyses were appropriate and generally controlled for relevant potential confounders.

Quantitative risk estimates from the eight studies are reported in Table 31. Eight of the 11 studies (excluding the study that used the duplicate sample but focused only on work-related physical activity[201]) reported risk estimates consistent with moderate or high levels of physical activity and suggesting a protective benefit from AD. The risk estimates did not always reach statistical significance once appropriate covariates were added or across both moderate and high levels of activity. This may point to insufficient sample size to detect a significant difference or confounding due to un-identified factors. Two studies reported results from analyses examining the interaction between physical activity and APOE genotype. These studies reported inconsistent results, with one reporting physical activity was most protective among carriers of the APOE e4 allele,[200] and the other study reporting the opposite result.[202] Similarly, results on whether there was a differential effect of physical activity on AD for males and females were not

consistent.[199,200] One study assessed the association between risk of AD and the combination of physical exercise and the Mediterranean diet.[85] Compared with individuals neither adhering to the diet nor participating in physical activity (low diet score and no physical activity; absolute AD risk of 19 percent), those both adhering to the diet and participating in physical activity (high diet score and high physical activity) had a lower risk of AD (absolute risk, 12 percent; HR 0.65 [95 percent CI 0.44 to 0.96]; P = 0.03 for trend).

A random-effects meta-analysis combining nine cohort studies is shown in Figure 7. Studies were significantly heterogeneous (Q = 23.25, df = 8, p = 0.003, I^2 = 66 percent). Higher levels of physical activity were associated with lower relative risk for incident AD (HR 0.72; 95 percent CI 0.53 to 0.98). An influence analysis that recalculated the summary HR iteratively, removing one study with each iteration, yielded summary HRs from 0.66 (95 percent CI 0.48 to 0.91) to 0.75 (0.54 to 1.05), suggesting that no single study had a large effect on the estimate of association.

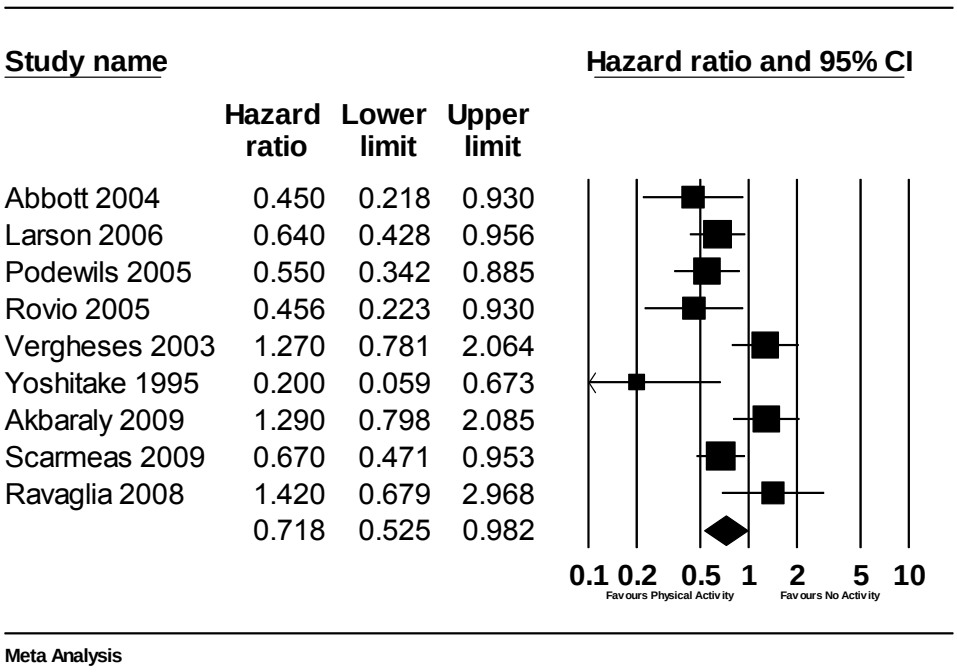

Figure 7. Meta-analysis of nine cohort studies on physical activity and risk of developing AD. Combined estimate is given in bottom row.

In conclusion, the results from the meta-analysis and the majority of studies reviewed here suggest that physical activity, particularly at high levels, is associated with lower risk of incident AD. However, there was substantial heterogeneity among the studies. The risk estimates from individual studies were not all statistically significant, and in some studies the risk estimate was in the direction indicating increased risk of AD. Differences among the studies in samples,

methodologies, and measures of exposure do not provide an obvious explanation for the inconsistent results. One point to consider when interpreting these results is that physical activity may be a marker for a generally healthier lifestyle and that these other healthy lifestyle factors may contribute to preserving cognition in later life. One of the studies described here addressed this point by examining the combination of physical activity and a Mediterranean diet on risk of AD.[85] Future work should consider this multi-factorial approach.

Table 31. Physical activity and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Andel et al., 2008[196]	Community cohort (twins) (3134)	31 years (mean) 197 AD	Time of exposure: Mid-life Self-report responses to the question: "How much exercise have you had from age 25 to 50?'' Responses were coded: 0 (hardly any exercise), 1 (light exercise such as walking or light gardening), 2 (regular exercise involving sports), or 3 (hard physical training)	NINCDS-ADRDA DSM	Age Sex Educational level Diet BMI Alcohol use Smoking Angina	Adjusted OR (95% CI) for risk of AD compared with hardly any exercise: Light exercise: 0.64 (0.41 to 1.00) Regular (moderate) exercise: 0.34 (0.14 to 0.86) Hard training: 0.65 (0.33 to 1.29)
Abbott et al., 2004[197]	Community cohort (2257)	7 years 101 AD	Time of exposure: Late-life Self-report responses to questions about the average amount of distance walked per day.	NINCDS-ADRDA DSM	Age APOE Baseline CASI Declines in activity since mid adulthood Physical performance score Education BMI Childhood years spent living in Japan Occupation Health conditions	Adjusted HR (95% CI) – reference is individuals who walked > 2 miles per day: Those who walked < 0.25 miles per day: 2.21 (1.06 to 4.57) Those who walked < 0.25 to 1 mile per day: 1.86 (0.91-3.79) Those who walked 1 to 2 miles per day: 1.88 (0.87-4.04)
Laurin et al., 2001Laurin,	Community cohort (4615)	5 years 194 AD	Time of exposure: Late life	NINCDS-ADRDA DSM	Sex Educational level Family history of	Adjusted OR (95% CI) for AD for levels of physical activity compared to no physical activity (adjusted for age, sex, and

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
2001[199]			Self-report responses to two questions about frequency and intensity of exercise for individuals who reported physical activity. Composite physical activity score categorized: 1) "Low" = less than weekly 2) "Moderate" = weekly 3) "High"= ≥ 3 times weekly		dementia Tobacco use Alcohol use NSAID use Daily living activities Clinical variables	education): Low activity: 0.67 (0.39 to 1.14) Moderate activity: 0.67 (0.46 to 0.98) High activity: 0.50 (0.28 to 0.90) ORs increased somewhat when males and females were examined separately and when additional covariates were added to the model, with the exception that the ORs decreased (even lower risk) for females with high levels of physical activity
Larson et al. 2006[198]	Clinical cohort (Group Health Co-operative, HMO) (1740)	Mean 6.2 years (SD, 2.0) 107 AD	Time of exposure: Late-life Self-report responses for the number of days per week during the past year the individual did the following activities for at least 15 minutes at a time: Walking, hiking, bicycling, aerobics or calisthenics Swimming, water aerobics, weight training Stretching, or other exercise. Responses dichotomized as "exercised regularly," defined as self-report of exercise ≥ 3	NINCDS-ADRDA DSM	Age Ethnicity Sex Educational level Baseline cognitive function Physical function Depression Health conditions Lifestyle characteristics Supplements APOE	Risk of AD for those who exercised regularly compared to those who did not exercise regularly: Age- and sex-adjusted HR: 0.64 (95% CI 0.43 to 0.96, p = 0.031) HR adjusted for all potential confounders: 0.69 (95% CI 0.45 to1.05; p = 0.081) Risk reduction associated with exercise was greater in those with lower performance levels. (p = 0.021 for interaction of exercise with performance-based physical function)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
			times/week, vs. "did not exercise regularly."			
Rovio et al. 2005[200]	Community cohort (1449)	Mean 21 years (SD 4.9) 76 AD	Time of exposure: Mid-life Self-report responses to: "How often do you participate in leisure-time physical activity that lasts at least 20-30 minutes and causes breathlessness and sweating?" Responses dichotomized: "Active" = active ≥ 2 times/week "Sedentary" = < 2 times/week	NINCDS-ADRDA DSM	Age Sex Educational level Followup time Locomotor disorders APOE Clinical variables Smoking status Alcohol use	Risk of AD for "active"' versus "sedentary": Adjusted OR: 0.35 (95% CI 0.16 to 0.80) Physical activity had same effect on both sexes APOE appears to be an effect modifier: among APOE carriers there is an association between physical activity and AD, but not among non-carriers (additive interaction RERI = 0.73,p = 0.02)
Rovio et al. 2007[201]	Community cohort (1449)	Mean 20.9 years (SD 4.9) 48 AD	Time of exposure: Mid-life Self-report responses to the questions: "How physically heavy is your work?" Responses dichotomized as sedentary vs. active groups. "How many minutes do you walk, bicycle, or have some other physical activity when you are going to and from work?" Categorized as:	NINCDS-ADRDA DSM	Race Educational level Followup time Locomotor symptoms Occupation Income at midlife Leisure physical activity APOE Vascular disorder Smoking status	Adjusted OR (95% CI) for risk of AD associated with high active vs. sedentary physical work activity: 1.90 (0.73 to 4.95) Adjusted OR (95% CI) for risk of AD associated with physical activity during commuting: No physical activity vs. moderate physical activity: 0.36 (0.13 to 0.96) High physical activity vs. moderate activity: 0.48 (0.09 to 2.58) No interactions with APOE

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
			1) not at all 2) ≤ 59 minutes 3) ≥ 60 minutes			
Verghese et al., 2003[194]	Community cohort (469)	Median 5.1 years 124 dementia, of which 86 were AD or mixed dementia	Time of exposure: Late-life Self-report of frequency of involvement in the following 11 physical activities: Playing tennis or golf, swimming, bicycling, dancing, participating in group exercises, playing team games such as bowling, walking for exercise, climbing more than two flights of stairs, doing housework, and babysitting Frequency of participation reported as "daily," "several days per week," "once weekly," "monthly," "occasionally," or "never." Responses used to create index: 7 points for daily participation; 4 points for participating several days per week; 1point for participating once weekly; and 0 points for participating monthly, occasionally, or never. Summed the activity-days for each	NINCDS-ADRDA DSM	Age Sex Educational level Medical illness Baseline Blessed test score Participation in other leisure activities	Adjusted HR for dementia associated with dancing (frequent versus rare): HR 0.24 (95% CI 0.06 to 0.99) No other physical activities showed a significant association with dementia Adjusted HR (95% CI) for dementia for 1-point increment in the physical activity scale: 1.00 (0.98 to 1.03) Adjusted HR (95% CI) for dementia using < 9 points on physical activity scale as comparison: 9 to 16 points: 1.44 (0.91 to 2.28) > 16 points: 1.27 (0.78 to 2.06)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
			activity to generate a physical-activity score, ranging from 0 to 77. Responses dichotomized as "rare participation" (once a week or less) versus "frequent participation" (several days a week or more).			
Podewils et al., 2005[202]	Community cohort (3041)	5.4 years 245 AD cases	Time of exposure: Late-life Self-reported information about frequency and duration during the previous 2 weeks of the following activities: Walking, household chores, mowing, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golfing, general exercise, and swimming. Activities converted to number of kilocalories (kcal) expended per week and number of activities per week	NINCDS-ADRDA	Age Race Sex Educational level Baseline cognitive status	Adjusted HR (95% CI) for AD for number of activities in previous 2 weeks versus 0 to 1 activity: 2 activities: 0.73 (0.49 to 1.08) 3 activities: 0.85 (0.57 to 1.29) ≥ 4 activities: 0.55 (0.34 to 0.88; p = 0.03) Adjusted HR (95% CI) for AD associated with number of kilocalories expended per week compared to < 248 kcal/week: 248 to 742 kcal/week: 1.07 (0.73 to 1.57) 743 to 1657 kcal/week: 0.92 (0.62 to 1.39) > 1657 kcal/week: 0.70 (0.44 to 1.13) P for trend = 0.08 Association only significant for non-e4 carriers. P trend for kcal/week = 0.01 and p trend for number of activities = 0.001.
Yoshitake et al., 1995[118]	Community cohort (577 at followup)	7 years 42 AD	Time of exposure: Late-life Self reported information about	NINCDS-ADRDA DSM	Age Sex Baseline cognitive status	Adjusted HR (95% CI) for AD for physically active group versus non-active group: 0.20 (0.06 to 0.68)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
			physical activity (four categories each for leisure and for work). Defined the physically active group as those including daily exercise during the leisure period or moderate to severe physical activity at work.			
Akbaraly et al., 2009[195]	Community cohort (5692)	4 years 105 AD cases	Time of exposure: Late-life Self-report of daily frequency physical activities that included doing odd jobs, gardening, and going for a walk	NINCDS-ADRDA DSM	Age Sex Study center (Dijon or Montpelier) Marital status Educational level Occupational grade Vascular risk factors: - Diabetes - HTN - High cholesterol - History of vascular disease Depressive symptoms (CES-D > 16) Physical function (instrumental ADL score > 0) Cognitive impairment (MMSE score < 24) APOE genotype	HR for AD compared to the lowest tertile of physical leisure activities: High tertile: 1.29 (95% CI 0.80 to 2.09) Mild tertile: 0.87 (95% CI 0.50 to 1.51)
Scarmeas et al.,	Community cohort	5.4 years	Time of exposure: Late-life	NINCDS-ADRDA	Age	Considered simultaneously, both high adherence to a Mediterranean-type diet and

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
2009[85]	(1880)	282 AD cases	Self-reported responses about number of times participating and number of minutes per time participating in 3 different categories of activities: vigorous (aerobic dancing, jogging, playing handball), moderate (bicycling, swimming, hiking, playing tennis), and light (walking, dancing, calisthenics, golfing, bowling, gardening, horseback riding). Estimation of adherence to a Mediterranean diet based on self-reported responses on a semi-quantitative food frequency questionnaire	DSM	Race Sex Educational level BMI Smoking Depression Leisure activities Comorbid medical conditions Baseline CDR score APOE Interval between 1st dietary and 1st physical activity measure Caloric intake	high physical activity level were associated with lower risk of AD Compared to low diet score: Middle diet score: HR 0.98 (95% CI 0.72 to 1.33) High diet score: HR 0.60 (95% CI 0.42 to 0.87); P = 0.008 for trend Compared to no physical activity: Some physical activity: HR 0.75 (95% CI 0.54 to 1.04) Much physical activity: HR 0.67 (0.47 to 0.95); P = 0.03 for trend
Ravaglia, et al., 2008[203]	Community cohort (also included institutionalized individuals) (749)	3.9 years 54 AD cases	Time of exposure: Late-life Self reported physical activity: (a) number of city blocks walked daily; (b) number of flights of stairs climbed daily; (c) frequency and duration of weekly participation during past year in	NINCDS-ADRDA DSM	Age Sex Educational level APOE Cardiovascular disease Hypertension Hyperhomo-cysteinemia Cerebrovascular	Physical activities were categorized into a dichotomous variable for the type of activity or the number of kilocalories expended in the activity. None of the categorizations of physical activity was significantly associated with incident AD. Some HRs were above 1.0 and some were less than 1.0.

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
			occupational, recreational and sport activity		disease Diabetes COPD Cancer ADL motor impairment	

Abbreviations: AD = Alzheimer's disease; ADL = activities of daily living; APOE = apolipoprotein E gene; BMI = body mass index; CASI = Cognitive Abilities Screening Instrument; CDR = Clinical Dementia Rating scale; CES-D = Center for Epidemiologic Studies Depression scale; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DSM = Diagnostic and Statistical Manual of Mental Disorders; HMO = health maintenance organization; HR = hazard ratio; HTN = hypertension; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; RERI = relative excess risk from interaction; SD = standard deviation

Other leisure activities. We did not identify any systematic reviews that examined the association between non-physical leisure activities and development of AD. We identified one eligible cohort study that assessed participation in a range of leisure activities, including those considered to be cognitive, social, or physical,[179] and one eligible cohort study that assessed activities that the authors of the study categorized as either social leisure or passive leisure activities.[195] The leisure activities assessed for each study are listed in Table 32. Some of the leisure activities in these studies overlapped with activities considered to be "cognitively engaging" in other studies,[192-194] so the results described here should be interpreted in conjunction with the findings for Question 1 for the "Cognitive Engagement" factor. The current two studies are summarized in Table 32; detailed evidence tables are provided in Appendix B. One of the studies used a sample drawn from a U.S. community,[179] and the other used a community sample from Europe.[195] Mean length of followup ranged from 2.9 to 4 years. Exposure status was based on self-report of current involvement in specific activities on either a daily or monthly basis. There was no objective validation of this method. Both studies used sample selection methods to minimize selection bias, but only one reported comparisons of baseline characteristics between those exposed and unexposed.[195] Investigators used standard criteria for the diagnosis of dementia and AD. They did not report whether the diagnosis was blind to exposure status; however, it is unlikely that details of involvement in these types of activities would be discussed during the diagnostic process. Analyses were generally appropriate and controlled for relevant potential confounders. One study reported results for overall dementia (not for AD),[179] while the other reported results specifically for AD.[195]

Akbaraly and colleagues[195] reported that more frequent participation in social leisure or passive leisure activities was not associated with reduced incidence of AD; the hazard ratios for the highest level of exposure for both social and passive leisure activities were in the direction of a lower risk of AD, but they were not statistically significant. In contrast, Scarmeas and colleagues[179] found that participation in more leisure activities was associated with a decreased risk of incident dementia. Grouping the leisure activities into categories showed that intellectual activities (RR 0.76; 95 percent CI 0.61 to 0.94), physical activities (RR 0.80; 95 percent CI 0.66 to 0.97), and social activities (RR 0.85; 95 percent CI 0.77 to 0.94) were all associated with reduced risk of incident dementia.[179] These results suggest that any leisure activity, regardless of whether it is cognitive, physical, or social in nature, may provide some protection against dementia. In addition, participation in a greater number of these activities may be key to their protective benefits.

These two studies differed in the types of leisure activities assessed, the number of AD or dementia cases, and also in how they characterized the exposure. One study used the frequency or time involved in each activity, which also indirectly reflected involvement in multiple activities,[195] while the other used just the number of activities in which the participant was involved.[179] Any of these differences may explain the discrepant findings between the two studies.

In conclusion, there is no consistent evidence indicating that involvement in leisure activities that are not solely cognitive or physical in nature is associated with lower risk of incident AD or dementia.

Table 32. Leisure activities and risk of developing AD

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Scarmeas et al., 2001[179]	Community cohort (1772)	Mean 2.9 years (range 0 to 7.2) 207 dementia (153 AD)	Self-reported participation in the following 13 activities: - Knitting or music or other hobby - Walking for pleasure or excursion - Visiting friends or relatives - Being visited by relatives or friends - Physical conditioning - Going to movies or restaurants or sporting events - Reading magazines or newspapers or books - Watching television or listening to the radio - Doing unpaid community volunteer work - Playing cards or games or bingo - Going to a club or center - Going to classes - Going to church or synagogue or temple One point given for participation in each of the above activities	NINCDS-ADRDA DSM	Ethnicity Sex Educational level Occupation Medical conditions	Number of leisure activities as a continuous variable in an age-stratified Cox model, higher scores were associated with a reduced risk of dementia: RR 0.89 (95% CI 0.84 to 0.94)

Study	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results
Akbaraly et al., 2009[195]	Community cohort (5692)	4 years 105 AD cases	Passive leisure activities: Self-report of frequency daily of watching television, listening to the radio, listening to music, and knitting/sewing Social leisure activities: Self-report of frequency monthly visiting or inviting friends or relatives	NINCDS-ADRDA DSM	Age Sex Study center (Dijon or Montpelier) Marital status Educational level Occupational grade Vascular risk factors: - Diabetes - HTN - High cholesterol - History of vascular disease Depressive symptoms (CES-D > 16) Physical function (IADL score > 0) Cognitive impairment (MMSE score < 24) APOE genotype	HR (95% CI) for passive leisure activities and AD with lowest tertile as reference: Mild: 1.02 (0.62 to 1.69) High: 0.68 (0.41 to 1.13) For social leisure activities: Mild: 1.06 (0.67 to 1.68) High: 0.70 (0.41 to 1.21)

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; CES-D = Center for Epidemiologic Studies Depression scale; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; HTN = hypertension; IADL = instrumental activities of daily living; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; RR = relative risk

Tobacco use. We identified two good quality systematic reviews, published in 2007 and 2008, that examined the association between tobacco use and the development of AD.[50,204] We decided to use only the systematic review by Anstey and colleagues[50] because compared to the other review[204] it used broader search terms and stricter inclusion criteria more consistent with those used by the present authors, reported detailed results from multiple exposure levels, and clearly identified the studies used in each analyses. The review included 10 prospective cohort studies published between 1995 and 2005.[64,104,105,118,205-210] The 10 studies included a total of 13,786 subjects; four were conducted in the United States, two in European countries, and one each in Canada, Australia, Japan, and China. Studies were selected that had at least two occasions of measurement, had AD as an outcome, had at least a 12-month followup period, and measured exposure to smoking at baseline. The number of individuals with AD versus other dementias was available for the majority of the studies. There was not a structured quality assessment of the studies reported in this systematic review; however, the strict inclusion/exclusion criteria provided an indirect assessment of quality, and the study characteristics for key design variables were reported. Length of followup ranged from 2 to 30 years. No information was provided on the followup rates in the studies. The covariate adjustment for most studies included at least age and education; many studies included additional covariates such as sex, APOE, biological measures, and health conditions. Selection of models to report from individual studies was determined first by the model with the smallest standard error and then on the model with the largest number of covariates. Exposure was determined by self-report, and smoking was classified as ever, current, former, or never smokers. All studies with AD as an outcome used DSM and/or NINDS-ADRDA diagnostic criteria.

Studies were combined using fixed-effect meta-analyses if there was no evidence of heterogeneity. If heterogeneity was present, random-effects models were used. Standard χ^2 tests using a p-value of 10 percent were used to examine heterogeneity. The small number of studies within each group of studies with compatible measures precluded investigation of heterogeneity, using meta-regression, subgroup analyses, or assessment of publication bias.

The results for the various exposure definitions and the outcome of AD are reported in Table 33. The studies that provided data for three smoking statuses (current, former, and never) provided data only for current-versus-never and former-versus-never comparisons. The authors of the review mathematically derived conservative estimates of the current-versus-former comparison from the current-versus-never and former-versus-never. To briefly summarize the main findings, current smokers were at greater risk of AD compared to either never smokers or former smokers. The results in Table 33 suggest a crude dose-response association, with the risk of AD progressively increasing from never smokers to former smokers to current smokers. Some caution is urged in interpreting the pattern of results in this way because different studies contribute to the relative risks for each of the comparisons. In addition, the mathematically derived relative risk for current versus former smokers is almost equal that of the comparison of current versus never smokers, a result that would not be expected if there were a dose-response effect.

Table 33. Smoking and risk of developing AD – results from studies reviewed by Anstey et al., 2007[50]

Comparison	Relative Risk (95% CI)
Current smokers versus never smokers (n = 4 studies)	1.79 (1.43 to 2.23)
Ever smokers versus never smokers (n = 3 studies)	1.21 (0.66 to 2.22)
Former smokers versus never smokers (n = 5 studies)	1.01 (0.83 to 1.23)
Current smokers versus former smokers (n = 4 studies)	1.70 (1.25 to 2.31)
Current smokers versus former and never smokers (n = 2 studies)	1.25 (0.49 to 3.17)

Abbreviation: CI = confidence interval.

The authors noted that one limitation of the study was that the former smokers group included a broad range of exposure periods. Unfortunately, there were not a sufficient number of studies with data on the number of smoking pack-years to use this as the exposure variable. Although publication bias was not assessed formally, the authors noted that 2 of the 10 studies did not focus on smoking, but rather the results on smoking were incidental to the aim of the study and additional data were obtained from the authors of the source studies. For this reason, one might conclude that the potential for publication bias was reduced. Quality ratings of the studies were not provided, but strict selection criteria may have increased the likelihood that only high quality studies were included in the review. The authors of the systematic review concluded that current smokers are at increased risk of AD.

We identified two additional eligible cohort studies published since the beginning of 2005.[211,212] These studies are summarized in Table 34; detailed evidence tables are provided in Appendix B. Both studies drew samples from the community, and one of them also included institutionalized individuals; one study was based on a U.S. sample and the other was conducted in Europe. At baseline, participants in both studies were non-demented. Length of followup ranged from a mean of 4 to 7 years. Both studies used self-report history of smoking obtained at baseline to characterize exposure. The studies used sample selection methods to minimize selection bias; however, neither study compared baseline characteristics to assess differences between exposed and unexposed. Both studies reportedly used standard criteria for the diagnosis of AD, but one of the studies did not use an informant report as part of the diagnostic process. Neither study noted whether the cognitive diagnoses were assigned blind to exposure status; however, the smoking analyses were not the primary outcome, so knowledge of exposure status may have had little effect on the outcome. Analyses were appropriate and controlled for relevant potential confounders, but neither study conducted a priori sample size calculations.

Both studies showed an increased risk of AD associated with current smoking compared to individuals who never smoked. They also showed that current smokers without an APOE e4 allele had an increased risk of AD, but there was no increased risk of AD associated with smoking for individuals with one or more e4 alleles.

Table 34. Tobacco use and risk of developing AD – recent cohort studies

Study	Design	Sample (n)	Followup/ Events	Exposure	Case definition	Confounding adjustment	Results*
Aggarwal et al., 2006[211]	Cohort	Community, including institutionalized individuals (1064 in present analysis)	0.4 to 6.9 years (mean 4.1; SD 0.92) 170 AD cases	Self-report smoking history	NINCDS-ADRDA	Age Sex Educational level Race Frequency of participation in cognitive activities APOE Time from baseline cognition	Adjusted ORs: Current smoker: 3.4 (1.44 to 8.01) Former smoker: 0.90 (0.47 to 1.70) Among individuals with one or more APOE e4 alleles: Current smoker: 0.57 (0.11 to 3.12) Former smoker: 0.27 (0.08 to 0.93) Among individuals with no APOE e4 allele: Current smoker: 4.32 (1.28 to 14.65) Former smoker: 1.37 (0.62 to 3.04)
Reitz et al., 2007[212]	Cohort	Community (6868)	Mean 7.3 years (SD 4.3) 555 AD cases	Self-report smoking history	NINCDS-ADRDA DSM	Age Sex Educational level Alcohol use APOE	Current smoker: 1.51 (1.10 to 2.08) Former smoker: 1.17 (0.90 to 1.52) Among individuals with one or more APOE e4 alleles: Current smoker: 1.06 (0.62 to 1.79) Former smoker: 1.08 (0.73 to 1.60) Among individuals with no APOE e4 allele: Current smoker: 1.95 (1.29 to 2.95) Former smoker: 1.10 (0.76 to 1.60)

* Reference group is never smokers.

Abbreviations: AD = Alzheimer's disease; APOE = apolipoprotein E gene; APOE e4 = e 4 allele of the apolipoprotein E gene; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; n = number of subjects; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; SD = standard deviation

In conclusion, the studies examining current smokers versus never smokers and/or former smokers consistently show an increased risk of AD associated with current smokers (although not all studies show a statistically significantly increased risk). However, former smokers do not appear to be at increased risk of AD. The authors of the review[50] noted that there were insufficient data to evaluate the duration of smoking among the current and former smokers or the duration of abstinence from smoking among former smokers. Thus, questions about the amount of time it takes a former smoker to return to the level of risk of a never smoker could not be addressed.

The evidence provided above refers only to smoking; the effects of nicotine itself may be different, as nicotine may aid specific cognitive functions such as attention, reaction time, and learning and memory tasks. We searched for systematic reviews and studies examining the association between nicotine and cognition, but (as described under Questions 3 and 4) we did not identify any eligible publications.

Alcohol use. We identified a single, good quality systematic review, published in 2009, that examined the association between alcohol use and the development of AD.[51] The review included nine prospective community cohort studies published between 2002 and 2006.[104,118,213-219] The nine studies included a total of 17,835 subjects; two were conducted in the United States, three in European countries, one in Canada, one in Japan, one in Korea, and one in China. Studies were selected that screened for dementia at baseline or adjusted for cognitive function at baseline, had at least a 12-month followup period, had AD as an outcome, and measured exposure to alcohol at baseline or during the followup period prior to the final followup examination. Study participants were non-demented at baseline. The number of individuals with AD versus other dementias was available for the majority of the studies. The meta-analysis reported was based on current use of alcohol, although some of the included studies also collected data on those who formerly used alcohol versus those who never used alcohol. There was not a structured quality assessment of the studies reported in this systematic review; however the strict inclusion/exclusion criteria provided an indirect assessment of quality, and the study characteristics for key design variables were reported. Length of followup ranged from 2 to 7 years. No information was provided on the followup rates in the studies. The covariate adjustment for most studies included at least age, sex, and education; many studies included additional covariates such as APOE, health behaviors, biological measures, and health conditions. The authors of the review noted that models with the largest number of covariates were given priority when determining the selection for inclusion in the report. Exposure was determined by self-report in all studies, but the categorization of extent of current and past alcohol use differed across the studies. For the meta-analyses, comparisons were made between drinkers versus non-drinkers, light to moderate drinkers versus non-drinkers, and heavy drinkers versus non-drinkers. All studies with AD as an outcome used DSM and/or NINDS-ADRDA diagnostic criteria.

Studies were combined using fixed-effect meta-analyses if there was no evidence of heterogeneity. If heterogeneity was present, random-effects models were used. Standard χ^2 tests using a P value of 10 percent were used to examine heterogeneity. The test for heterogeneity was significant for AD for light to moderate drinkers versus nondrinkers $\chi^2_{[5]} = 11.43$, $P = 0.04$). The test for heterogeneity for heavy drinkers versus nondrinkers was not significant. Publication bias was not formally assessed.

The results for the various exposure definitions and the outcome of AD are reported in Table 35. The definition for light to moderate drinker varied across the studies and ranged from 1 to 2

drinks per week as a minimum to 13 to 28 drinks per week as a maximum. To summarize the main findings, all drinkers combined had a lower risk of AD compared to non-drinkers. Light to moderate drinkers also had a lower risk of AD compared to non-drinkers. Three studies provided results by sex and reported that light to moderate alcohol use was protective for AD in both males and females. However, heavy/excessive drinkers showed no difference in risk compared to non-drinkers.

Table 35. Alcohol use and risk of developing AD – results from studies reviewed by Anstey et al., 2009[51]

Comparison	Relative Risk (95% CI)
Light to moderate drinkers versus non-drinkers (n = 6 studies)	0.72 (0.61 to 0.86)
Heavy/excessive drinkers versus non-drinkers (n = 4 studies)	0.92 (0.59 to 1.45)
Drinkers versus non-drinkers (n = 2 studies)	0.66 (0.47 to 0.94)
Male light to moderate drinkers versus male nondrinkers (n = 3 studies)	0.58 (0.45 to 0.75)
Female light to moderate drinkers versus female nondrinkers (n = 3 studies)	0.83 (0.81 to 0.85)

Abbreviation: CI = confidence interval

The authors noted that the study of alcohol use as a risk factor for late-life health outcomes is complicated by variation in the type of beverage used and the criteria for measuring and categorizing quantity. In addition, the present meta-analyses (and many other studies) are limited to current use of alcohol only, but alcohol patterns may change over a lifetime, and former drinkers may differ from lifetime abstainers. Five of the studies included in the systematic review either for AD or for cognitive decline collected data on former drinkers compared to lifetime abstainers.[217-221] The cognitive outcomes for these studies were varied and included AD, dementia, and cognitive decline. Three of the studies[218,219,221] showed no difference in the associations between cognitive outcome and former drinkers compared to lifetime abstainers. But the results from two other studies[217,220] indicated that former drinkers account for much of the risk of cognitive impairment among non-drinkers; this suggests many former drinkers may have stopped drinking for reasons that also predispose to cognitive impairment, such as health problems. Although publication bias was not assessed formally, the systematic review authors noted that they included studies from article reference lists and articles that did not focus on alcohol use, but in which alcohol use was a covariate. For this reason, one might conclude that the potential for publication bias was reduced. Quality ratings of the studies were not provided, but strict selection criteria may have increased the likelihood that only high-quality studies were included in the review.

The systematic review authors concluded that light to moderate alcohol use in late life was associated with an attenuated risk of AD. They further concluded that it was not clear whether these results reflect selection effects in cohort studies that begin in later life, a protective effect of alcohol consumption throughout adulthood, or a specific benefit of alcohol in late life. The review did not find an increased risk of AD among individuals who drank heavily, but the authors speculated that this may be due to selection bias given the age of the samples.

We did not identify any additional eligible cohort studies published since June 2006.

In conclusion, individuals who drink light to moderate amounts of alcohol in late life appear to be at reduced risk of AD; however further research is needed to determine whether this

association is due to confounding factors. For example, there is some evidence to suggest that those who continue to use alcohol in late life are healthier in general which may itself lead to a lower risk of dementia.

Toxic Environmental Exposures

We identified one good quality systematic review of occupational risk factors for Alzheimer's disease, focusing on the associations between AD and pesticides, solvents, electromagnetic fields, lead, and aluminum in the workplace.[52] The review included 21 case-control studies and three cohort studies published between 1984 and 2003. Although case-control studies are a weaker design than cohort studies for establishing causality, we included case-control studies for this factor because of the paucity of data from cohort studies. Further, exposures to specific toxic substances are relatively uncommon and would require very large sample sizes to have sufficient power to detect an effect in general community samples. The number of studies and subjects for each risk factor is summarized in Table 36. Three of the publications reported on different exposures from the same study population. Studies were included if it was possible to calculate a relative risk for AD; if the exposure occurred in the workplace; and if the clinical diagnosis of AD was based on NINCDS-ADRDA, DSM, or ICD criteria. Two epidemiologists completed data abstraction and quality assessments independently; disagreements were resolved by consensus. Study quality was assessed using a 39-item assessment tool for case-control studies and a 30-item measure for cohort studies. A global quality index was calculated for each study and scored as the percentage of the maximum possible value achieved. Results were described qualitatively.

Table 36. Toxic environmental factors and risk of developing AD – characteristics of studies reviewed by Santibanez et al., 2007[52]

Risk Factor	Studies*	Subjects*	Countries
Solvents	10 case-control 1 cohort	3748 694	N. America (6), Western Europe (2), Asia (2) Canada
Electromagnetic fields	6 case-control 1 cohort	6205 20,068	U.S.A. (4), Western Europe (2) U.S.A.
Pesticides	4 case-control 2 cohort	1471 2201	Canada (2), U.S.A. (1), Australia (1) Canada (1), France (1)
Lead	6 case-control	2182	U.S.A. (4), U.K. (1), Australia (1)
Aluminum	3 case-control	1056	U.S.A. (1), U.K. (1), Australia (1)

* Some studies examined multiple factors, and number of studies and subject counts are included for each exposure. Therefore, the study count in this table exceeds the 22 studies identified.

For the 24 studies, the median global quality index was 36.6 percent. The most common quality problems were: misclassification of the exposure (18/24), surrogate informants (12/17), misclassification of the disease (11/24), and selection bias in 10 studies. Study quality was judged to be higher for pesticide exposures. Two cohort studies reported higher adjusted relative risks for AD with exposure to defoliants and fumigants (RR 4.35; 95 percent CI 1.05 to 17.90)[222]

and pesticides in men (RR 2.39, 1.02 to 5.63).[223] Two higher quality case-control studies[137,224] found small, non-statistically significant associations between pesticides and AD.

Other exposures were reported to show less consistent associations. Of the 11 studies evaluating solvents, two found a statistically significant association with AD. However, these two studies were from the same population base. The single cohort study evaluating solvent exposure[222] did not find an association with AD (RR 0.88; 95 percent CI 0.31 to 2.50). Studies of lead exposure were all case-control design and assessed as low quality; none showed a statistically significant association with AD. One study of aluminum exposure was a higher quality case-control study and found no association with AD (RR 0.95; 95 percent CI 0.5 to 1.9).[225] Similarly, the two lower quality case-controls studies[226,227] did not find any association between aluminum and AD.

Our search identified two additional studies on the exposures of interest, one evaluating aluminum exposure and one evaluating blood mercury levels. Rondeau et al.[228] followed a community sample of 1925 non-demented adults, age 65 and older, for a mean of 11.3 years. Aluminum exposure was estimated using a food frequency questionnaire that assessed tap water consumption, coupled with chemical analysis of aluminum levels in drinking water. The estimate of aluminum intake is not well validated, and followup rates were not given. The risk of AD was increased for aluminum intake ≥ 0.1 mg/day (RR 1.34; 95 percent CI 1.09 to 1.65); no dose-response relationship was observed. This observation of elevated risk differs from the finding of no association in three previous case-control studies. Using a subgroup from the Canadian Study of Health and Aging (15 percent of the cohort), Kroger et al.[81] used a nested case-control design to evaluate the association between blood mercury levels and AD. After a median of 4.9 years, individuals in the 3rd (OR 0.41; 95 percent CI 0.23 to 0.74) and 4th quartiles of exposure (OR 0.56, 0.32 to0.99) were at lower risk for AD. However, the relatively low participation rate may have introduced significant selection bias. We did not identify any studies on Agent Orange or gulf war syndrome.

In summary, few cohort studies have examined the association between toxic-environmental exposures and risk of AD. Most case-control studies have important methodological limitations that may bias the results. Among the exposures considered, only pesticides showed a consistent association with AD.

Genetic Factors

After age, family history is the strongest risk factor for the development of Alzheimer's disease. As early as the 1920s, there were reports of a few families with many individuals with AD across more than one generation, suggesting a genetic contribution to the disease (for a review, *see* Kennedy et al., 1994[229]). Twin studies provided further support for the role of genes in the etiology of AD. Heritability is defined as the proportion of disease liability attributable to genes, and it can be estimated from the difference in disease concordance rates for monozygotic twin pairs compared to dizygotic pairs. Estimates of heritability of AD from twins studies have ranged from 0.33 to 0.74,[230-232] indicating a moderate genetic contribution. The genetics of AD, however, are complex, with fully penetrant autosomal dominant mutations responsible for early-onset disease (onset prior to 60 years of age) and other genetic susceptibility factors responsible for the much more common late-onset disease (> 95 percent of cases). Mutations in three different genes have been identified that cause early-onset AD, but these account for a small minority of individuals with AD. Disease-causing mutations in these genes, amyloid precursor

protein (APP) gene and presenilin 1 and 2, are completely penetrant, and most individuals who inherit these mutations become symptomatic in their thirties or forties. These three genes also play a role in amyloid formation, strengthening the argument that amyloid deposition is a key factor in disease pathogenesis. Individuals who inherit a disease-causing mutation in one of these genes will develop AD unless they die prematurely from other causes. Genetic testing is commercially available for each of these early-onset disease genes. In contrast to early-onset AD, no classically Mendelian genetic influences have been found for the much more common late-onset AD.

The literature on genetic influences on late-onset AD is extensive. AlzGene, a regularly updated genetic database that compiles association studies on AD (http://www.alzgene.org/), reports data from 1355 studies examining 660 genes (Website updated January 29, 2010; accessed January 31, 2010).[53] AlzGene includes only studies published in peer-reviewed journals and performs meta-analyses on genetic polymorphisms that have been examined in at least four case-control samples. Meta-analyses are updated as more data are published, but family-based studies are not included in meta-analyses. Odds ratios and 95 percent confidence intervals are calculated for all polymorphisms with minor allele frequencies greater than one percent in healthy controls using a random-effects model with weights that incorporate within- and between-study variance. Data are presented for all studies and then separately after excluding studies in which in which the Hardy-Weinberg equilibrium criteria have not been met. To avoid including overlapping data, usually only the largest sample is included for analysis.

The meta-analyses performed in AlzGene are graded based on the amount of data available for a polymorphism, consistency of replication, and an assessment of bias. The data are graded from "A" to "C" based on the number of minor alleles in the case and control population. A grade of A requires > 1000 minor alleles, B between 100 and 1000, and C < 100. Consistency of replication is determined by I^2 point estimates: A = < 25 percent; B = 25 to 50 percent; and C = > 50 percent. Sources of bias that are considered include errors in phenotyping, genotyping, and population sources, as well as publication bias. Publication bias is assessed with a Begg-modified funnel plot depicting allele-specific ORs for each study versus its standard error on a semi-logarithmic scale. Summary ORs from meta-analyses are also graded based on their deviation from 1.0. Studies with summary ORs < 1.15 or ORs > 1.15 with evidence of publication bias receive a grade of C, acknowledging that occult biases and selective reporting may invalidate the proposed association. Studies that lose statistical significance after exclusion of the original publication or studies violating Hardy-Weinberg equilibrium are also given a grade of C. An overall assessment of association credibility is based on the overall score. Credibility is "strong" if a gene received three A grades; "moderate" if it receive at least one B grade and no C grades; and "weak" if it receives any C grades.

Apoliprotein E (APOE = gene; ApoE = protein) is the single most-validated genetic susceptibility factor in AD (overall AlzGene grade A). APOE has three common polymorphisms (e2, e3 and e4) that introduce an amino acid change in APOE. Inheriting one or two copies of APOE e4 increases the risk of developing AD in a dose-dependent fashion, while inheriting an e2 allele reduces risk. Case-control studies examining the association of APOE and AD are reported for Caucasian (28 studies), Asian (5 studies), African-descent (2 studies), Hispanic (1 study), and other or mixed origin populations (1 study). All studies reported increased risk of AD in subjects with APOEe4. A meta-analysis of 38 studies by AlzGene produced a summary OR of 3.68 (95 percent CI 3.30 to 4.11) for the e4 versus e3 alleles. The lower limit confidence interval excluded 1.0 in 36 of the 38 studies included in the analysis. A meta-analysis of 37 studies

examining the association of APOE e2 on the development of AD demonstrated a protective role for this allele (summary OR 0.621; 95 percent CI 0.456 to 0.85). The studies used for the AlzGene meta-analysis were originally compiled and analyzed by Farrer et al.,[233] with some data removed because they were derived from family studies, not published in English, or concerned unpublished genotype data. The results reported by Farrer and colleagues were qualitatively identical to the subsequent AlzGene analysis. They also provided summary ORs for the risk of developing AD for each genotype compared to the reference genotype APOE e3/e3; these were (OR; 95 percent CI): e2/e4, 2.6 (1.6 to 4.0); e3/e4, 3.2 (2.8 to 3.8); e4/e4, 14.9 (10.8 to 20.60); e2/e2, 0.6 (0.2 to 2.0); and e2/e3, 0.6 (0.5 to 0.8). No other susceptibility gene in AD approaches the statistical level of APOE. The literature suggests that there are racial and ethnic differences in the strength of the association between APOE genotype and AD. The APOE e4 association with AD is stronger in people of Japanese ancestry and weaker among African-Americans and Hispanics than among Caucasians, but there was significant heterogeneity in the ORs in studies of African-Americans ($p < 0.03$). APOEe2 also appears to be associated with protection from AD in Asians (OR for e2 vs. e3 0.548; 95 percent CI 0.277 to 1.08). Additional studies in African-Americans, Asians, and Hispanics are needed to establish a definitive risk estimate. The APOE e4 effect is age-dependent, with a major contribution to risk in people between the ages of 40 and 90 years, but the effect diminishes after the age of 70.

Nine other gene polymorphisms received a grade of A using AlzGene criteria. Clusterin (CLU), also called apolipoprotein J, located on chromosome 8, has been linked to AD in nine case-control samples. The OR for all samples was less than 1, with a summary OR for all studies of 0.86 (95 percent CI 0.82 to 0.89). A publication of these findings by two groups in separate GWAS studies involving approximately 30,000 subjects identified CLU rs11136000 as the single nucleotide polymorphism (SNP) with the greatest OR, other than APOE ($P = 1.4 \times 10^{-9}$ and $P = 7.5 \times 10^{-9}$ in the two studies.[234,235] By comparison, the P value for the most significant SNP in the APOE locus in one of the studies was 1.8×10^{-157}.[234] CLU expression is increased in a number of pathologic conditions involving brain injury or inflammation and binds soluble amyloid beta peptide, which may be relevant to AD pathogenesis. Phosphatidylinositol binding clathrin assembly protein (PICALM; also known as clathrin assembly lymphoid-myeloid leukemia gene [CALM]), located on chromosome 11, was also identified in a GWAS analysis of more than 16,000 individuals and received an A grade in AlzGene.[234] The OR for PICALM was less than 1.0 in 6 of 6 case-control samples examined, and in 5 of 6 samples the 95 percent CI excluded 1.0. The AlzGene summary OR for association of PICALM with AD was 0.87 (95 percent CI 0.83 to 0.91). PICALM is located on chromosome 11, is involved in clathrin-mediated endocytosis, and may play a role in synaptic vesicle fusion. Synaptic density is correlated with cognitive decline in AD, suggesting that this may be relevant to pathogenesis. Sortilin-related receptor (SORL1) is a low-density lipoprotein receptor relative located on chromosome 11 that has been associated with risk of AD. An AlzGene meta-analysis of 21 studies reported an OR of 1.10 (95 percent CI 1.03 to 1.71), with $I^2 = 33$. A locus on chromosome 14 called GWA 14q32.13 was identified as associated with AD in five studies. The meta-analysis OR for GWA 14q32.13 was 0.84 (95 percent CI 0.77 to 0.93). No associated gene has been identified with this polymorphism. Tyrosine kinase, non-receptor 1 (TNK1) has been examined in five case-control populations involving 10,920 people. Three samples showed a positive association of TNK1 with AD with 95 percent CIs excluding unity, two showed a trend, and one had an OR > 1. A meta-analysis of five datasets of TNK1 by AlzGene produced a summary OR of 0.84 (0.76 to 0.93). Angiotensin 1 converting enzyme (ACE) has been examined

in 57 case-control studies, with 20 studies showing positive results, 6 trending positive, and 22 showing negative results. Separate analysis was not available for six studies. A meta-analysis of ACE polymorphism rs1800764 in five datasets found a summary OR of 0.83 (95 percent CI 0.72 to 0.95), suggesting a protective effect for genetic variants in this gene. Two other single-nucleotide polymorphisms (SNPs) within this gene also produced significant results in meta-analysis.

Inflammation has been implicated in the pathogenesis of AD, and interleukin 8 (IL8) has been examined as a candidate gene in four case-control studies. A meta-analysis of these four studies reported an OR of 1.27 (95 percent CI 1.08 to 1.50; $I^2 = 0$), suggesting that different genotypes of IL8 modify an individual's risk of developing AD. The low-density lipoprotein receptor (LDLR), located on chromosome 19, has also been identified as a genetic modifier of AD. An AlzGene meta-analysis of four studies found an OR of 0.85 (95 percent CI 0.72 to 0.99). A caveat about the validity of ORs determined by meta-analysis is necessary here. The final gene with an AlzGene grade of A is Cystatin C. Cystatin C is a member of the cystatin gene family that contains proteins with cysteine protease activity; it has been examined in 19 case-control studies. Six studies reported an association, and 10 studies were negative. A meta-analysis of four datasets found a summary OR of 1.28 (95 percent CI 1.04 to 1.56) for the association of cystatin C with AD. It should be noted that meta-analysis ORs can be skewed by publication bias, producing inflated estimates if negative studies are less likely to be published.

A number of genome-wide association studies (GWAS) involving thousands of patients and hundreds of thousands of polymorphisms have been performed in AD, but apart from the studies identifying CLU and PICALM noted above, most have identified genetic variants of marginal statistical significance. Almost all AD GWAS have confirmed the association between the region containing APOE and AD, but detection of other polymorphisms has varied between studies despite regular use of validation sets to confirm results. Variability in results between studies could be the result of differences in populations or could be caused by spurious associations as the result of multiple hypothesis testing. At present, most GWAS results are best viewed as suggestive, with need for independent confirmation and demonstration of biological relevance to disease pathogenesis.

In summary, autosomal-dominant, early-onset AD is associated with mutations in three genes. APOE is the only well-validated susceptibility gene for late-onset AD, but a number of promising candidates have been identified, including those listed above. Additional data are necessary to confirm the relationship of these genes with AD and to demonstrate their biologic relevance to pathogenesis.

Key Question 2 – Factors Associated with Reduction of Risk of Cognitive Decline

Key Question 2 is: What factors are associated with the reduction of risk of cognitive decline in older adults?

Nutritional and Dietary Factors

B vitamins and folate. We identified five eligible cohort studies that examined the association between folate and B vitamins and cognitive decline.[56,236-239] These studies are

summarized in Table 37; detailed evidence tables are in Appendix B. All five studies reported either continuous variable outcomes or multiple levels of categorical outcome (e.g. quintiles). Three of the studies used community samples in the U.S.,[56,236,238] one used a community sample in Europe,[239]and the fifth used a clinical sample in Europe.[237] Two studies were based on the same sample, but one used niacin[56] and the other used folate and B12 levels[236] to predict cognitive decline. For all studies, participants were non-demented at baseline. The length of followup ranged from 5.5 to 10 years. All studies used sample selection methods to minimize selection bias. Three of the studies used plasma/serum levels of B vitamins and folate.[237-239] The other two studies estimated dietary and supplement intake of B vitamins and folate based on self-reported information collected using modified Harvard food frequency questionnaire. This group has previously reported results from a study that aimed to validate food frequency questionnaires. Three studies compared baseline characteristics between those exposed and unexposed.[56,236,239] The case definitions and measures of cognitive change for the studies are described in Table 37. The analyses appear generally appropriate, and most controlled for relevant potential confounders, including homocysteine and the other predictor variables (i.e., folate, B vitamins). None of the studies conducted a priori sample size calculations.

One study examined the association between niacin (B3) and cognitive change over time.[56] Investigators reported that higher dietary intake of niacin was generally associated with a modest protective effect on cognition; however, the results were only significant in subgroups of individuals without stroke or myocardial infarction or individuals with baseline cognitive scores in the upper 85 percent of the sample. When total niacin intake, including supplements, was evaluated there was no significant association between niacin intake and cognitive decline. The findings on folate were in opposite directions, with one study that used self-reported intake of nutrients reporting that higher levels of folate were associated with higher rates of cognitive decline,[236] and another study that used plasma levels of folate reporting that low levels of folate were associated with greater cognitive decline.[238] A third study that used serum levels of folate did not show any association between folate levels and cognitive change.[237] In general, the studies did not show any association between either B12 or B6 and cognitive decline, except in select subsamples.[236] In addition, there were inconsistent findings for the association between cognitive decline and holotranscobalamin and methylmalonic, markers that are related to B12 levels and function. One study showed no association between these markers and cognitive change,[239] while another[237] reported that doubling holotranscobalamin levels resulted in a slower rate of decline on the MMSE, and a doubling of methylmalonic acid levels resulted in a more rapid rate of decline. An explanation for the discrepancy in findings using plasma markers for B12 is not obvious, as the measures of central tendency for the baseline levels of the markers were not markedly different between the studies. The studies did differ in the source of the sample, with one being a community sample and the other being a clinical registry. In addition, the cognitive measures used to measure change differed between the studies; inconsistent results have frequently been reported both within and between studies on many exposures for different cognitive measures.

In conclusion, there is no consistent evidence to support an association between cognitive decline and exposure to niacin, folate, B12, or markers for B12 based on estimated intake or plasma levels of these factors. The preponderance of the limited studies on these exposures reports no association between these factors and cognitive change over time. Inconsistencies in the findings reported here may be due to a number of factors, including differences in both the types and quality of the exposure, the outcome measures, and sample characteristics.

Table 37. B vitamins and folate and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Morris et al., 2004[56] (Same sample as Morris et al., 2005[236])	Community cohort (3718)	5.5 years (median)	Estimates of total intake of niacin (B3) during the previous year were calculated from self-report responses on a modified Harvard food frequency questionnaire	Global composite index of scores on the MMSE, the immediate and delayed recall of the East Boston Story, and the oral version of the Symbol Digit Modalities Test	Age Race Sex Educational level APOE Time between assessments Sample weights Vitamin E Vitamin C Beta-carotene Multiple vitamin use DM HTN Smoking Alcohol use Stroke Heart disease Folate	Food intake of niacin had a linear protective effect on cognitive decline, but in fully adjusted model did not reach statistical significance (beta-coefficient= 0.017; SE = 0.011; p = 0.12). When those with stroke or MI (beta-coefficient = 0.035; SE = 0.010; p = 0.002) or low cognitive scores (beta-coefficient = 0.025; SE = 0.011; p = 0.03) were excluded, the results reached statistical significance. Total intake of niacin (including supplements) had no significant association with cognitive change over time.
Morris, et al., 2005[236] (Same sample as Morris et al., 2004[56])	Community cohort (3718)	5.5 years (median)	Estimates of total intake of folate and vitamin B12 during the previous year were calculated from self-report responses on a modified Harvard food frequency questionnaire	Global composite index of scores on the MMSE, the immediate and delayed recall of the East Boston Story, and the oral version of the Symbol Digit Modalities Test	Age Race Sex Educational level Time between assessments Vitamin E Vitamin C Multivitamin	Total intake of folate: Upper two quintiles declined slightly faster than lowest quintile (p value for 5th quintile = 0.002; trend p = < 0.001) Folate intake from food: Higher quintiles generally declined slightly faster than lowest quintiles (p value for 5th quintile = 0.02; trend p = 0.04) Intake of vitamin B12, with or without vitamin supplementation, was not significantly associated with cognitive change. There was a

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
						significant interaction between total intake of B12 and older age (P for interaction = 0.009), in which the rate of decline for an average 80-year-old who consumed a supplemental dose of 20 µg/day of vitamin B12 was 25% slower than the rate of a similar person who consumed the recommended dietary allowance of 2.4 µg/day.
Clarke et al., 2007[237]	Clinical cohort – from general medicine clinical registry (691 analytical sample)	10 years	Serum levels of B-12, folate, holotrans-cobalamin (the biologically active fraction of vitamin B-12) and methylmalonic acid (an indicator of vitamin B-12 function) were used as markers of vitamin B-12 status	Change in MMSE over time	Age Sex Smoking Vascular disease Systolic BP Education APOE Levels of other vitamins being assessed	Only holotranscobalamin and methylmalonic acid levels showed a significant association with cognitive change over time. Doubling holotranscobalamin levels resulted in an additional change in MMSE of 0.59 (0.30 to 0.86) points. Doubling methylmalonic acid levels resulted in an additional change in MMSE of -0.65 (-0.98 to -0.32) points. B12 and folate did not show a significant association with cognitive change.
Kado et al., 2005[238]	Community cohort (499 analytical sample)	7 years	Plasma levels of folate, B6 and B12	Summary cognitive score of measures assessing confrontational naming, delayed recall of items named, spatial recognition memory, concept similarities, and constructional praxis copying	Age Sex Education Baseline physical function Smoking Plasma levels of other predictors (B6, B12, folate, homocysteine)	In multivariate models that included homocysteine and the vitamins together in the same model, only low folate level predicted cognitive decline (risk ratio -1.60; 95% CI 1.01 to 2.31; P = 0.04). Neither B6 nor B12 levels were associated with cognitive change over time.
De Lau, et al., 2009[239]	Community cohort (1019)	7 years	Plasma B12 and transport (metabolites transcobolamin and holotrans-coboloamin, methylmalonic acid)	Longitudinal decline on an abbreviated Stroop test, verbal fluency test, Letter-Digit Substitution Task,	Age Sex Education Creatinine Homocysteine	No association was observed between any of the studied variables (including plasma B12 analyzed by quintiles) and rate of cognitive decline during followup. Specific results not shown in publication.

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
				Memory Scanning Test, 15-word memory test Combined tests created summary scores for psychomotor speed, memory, and global cognition	Folate DM BP Alcohol use Smoking Vitamin supplements Depression Carotid intima-media thickness	

Abbreviations: APOE = Apolipoprotein E gene; BP = blood pressure; CI = confidence interval; DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction; MMSE = Mini-Mental State Examination; SE = standard error

Other vitamins. We identified eight eligible cohort studies that examined the association between cognitive decline and vitamins C or E, beta carotene or flavonoids.[67,70,240-245] This summary will focus on the two studies with categorical outcomes.[67,244] A brief overview of the other studies using continuous outcomes of decline will be given, but a detailed review of these studies will not be provided because they do not change the conclusion from the two studies with categorical outcomes. The two studies reporting categorical variable outcomes are summarized in Table 38; detailed evidence tables for all of the studies are in Appendix B. One of the studies used a community sample in Europe,[244] and the other used a Canadian sample comprised of both community and institutionalized individuals.[67] One study stated that participants were non-demented at baseline,[67] and it is assumed here (although not explicitly stated by study investigators) that the participants were non-demented at baseline in the other study.[244] The length of followup ranged from 3 to 5 years. One study used sample selection methods to minimize selection bias.[244] The other study[67] used selection methods that partially addressed selection bias because they used a subsample from a larger cohort study, of which a disproportionate segment of the sample was at relatively high risk of cognitive impairment; part of this study sample was drawn from institutionalized participants (20 percent), and part from community participants. One study[244] used self-reported information to estimate food and supplement intake of vitamins C and E, beta carotene, and flavonoids. The other study used self-reported vitamin supplement use confirmed by inspection of medication container for the community residents and medical records for the institutionalized participants.[67]

One study compared baseline characteristics between those exposed and unexposed.[67] The case definitions for the studies are described in Table 38. The analyses appear generally appropriate and were controlled for relevant potential confounders. Neither study conducted a priori sample size calculations. One study reported no association between cognitive decline and vitamins E or C, beta carotene, or flavonoids.[244] The other study reported no association between cognitive decline and vitamins E or C separately, but did show a protective association for any vitamin use and combinations of multivitamins and vitamins C and E.[67]

To briefly summarize the studies reporting continuous outcomes of cognitive decline, we note that two studies were based on the same sample, with one reporting the association between cognitive decline and vitamins C and E,[242] and the other adding NSAIDs to the list of predictors.[240] Another two studies were based on the same sample with some differences in how vitamin E intake was estimated.[70,241] Two studies defined exposure levels using blood samples,[243,245] and the others based exposure levels on self-reported information. Four of the studies stated that participants were non-demented at baseline,[70,240-242] and it is assumed here that the vast majority of subjects in the other two studies[243,245] were non-demented at baseline based on the relatively young mean baseline age. Of the six studies defining cognitive decline as a continuous measure, only two studies that were based on the same sample reported a protective effect of vitamin E (but not vitamin C) on cognition.[70,241] However, for one of these studies,[241] the risk estimates for vitamin E and cognitive decline were not consistently in the same direction for all quintile levels of vitamin E.

In conclusion, the findings on vitamins E and C, beta carotene, and flavonoids provide no consistent support for a protective association between these nutrients and cognitive decline.

Table 38. Other vitamins and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Kalmijn et al., 1997[244]	Community cohort (342)	3 years	Estimates of intake of beta carotene, vitamins C and E, and flavonoids were calculated based on self-reported responses provided on a cross-check dietary history interview administered by a dietician. This information was based on food consumption pattern during the preceding 2 to 4 weeks Information combined for interviews 5 years preceding baseline and baseline	Cognitive decline defined as > 2-point decline	Age Educational level Smoking Alcohol use Energy intake Baseline cognitive status	No association between cognitive decline and intake of vitamins E and C, beta carotene, and flavonoids. P values for trend ranged from 0.09 to 0.7
Maxwell et al., 2005[67]	Community cohort (but also some nursing home residents) (894)	5 years	For non-institutionalized individuals, self-reported information on supplemental vitamin E and C use. Sometimes confirmed by review of medication bottle. For institutionalized individuals information on supplemental vitamin E and C use from medical record	Cognitive decline defined as a decrease ≥ 10 points on the 3MS from Time 1 to Time 2	Age Sex Educational level Blood pressure Baseline cognitive status Institutional residence	Cognitive decline: Vitamin E and C and/or multivitamin use associated with lower risk of cognitive decline (OR 0.51, 95% CI 0.29 to 0.90) Any vitamin use associated with lower risk of cognitive decline (OR: 0.57; 0.34 to 0.93) Vitamin E alone was not associated with cognitive decline (OR 0.64; 0.08 to 5.41) Vitamin C alone was not associated with cognitive decline (OR 0.83; 0.29 to 2.39)

Abbreviations: 3MS = Modified Mini-Mental State Examination; CI = confidence interval; OR = odds ratio

Gingko biloba. We identified no systematic reviews or studies evaluating the use of gingko biloba and risk of cognitive decline.

Omega-3 fatty acids. We identified two good quality systematic reviews evaluating the association between omega-3 fatty acids and risk of cognitive decline.[29,30] We discuss the more recent (2009) review by Fotuhi et al.[29] The review included three cohort studies published between 2003 and 2007. The three studies included a total of 4174 subjects; one each was conducted in the United States, France, and The Netherlands. Prospective observational studies were selected that addressed the specific association between any form of omega-3 fatty acids and cognitive change in participants age 65 or older. There was not a structured quality assessment of studies reported in this systematic review; however, study characteristics for key design variables were reported, and study selection criteria focused the review on higher quality studies. In two studies, cognitive testing at baseline excluded participants with dementia, and the third study recruited normal volunteers. Length of followup ranged from 4 to 6 years. No information was given on followup rates. Covariate adjustment included age, sex, education, and baseline cognitive function. Omega-3 fatty acid intake was estimated by dietary histories in two studies;[246,247] the third[248] measured erythrocyte membrane fatty acid content. Dietary histories were used in one study to classify exposure as the number of fish-containing meals per week and in the other study to estimate the levels of DHA and EPA from fish and other sources. Because of significant heterogeneity in study design, results were synthesized qualitatively. Adjusted results were reported and are summarized in Table 39. Each of the three studies showed an association between greater exposure and less cognitive decline.

The authors of the systematic review concluded that the existing evidence favors a role for long chain omega-3 fatty acids in slowing cognitive decline in older adults.

Table 39. Omega-3 fatty acids and risk of cognitive decline – study characteristics and results from studies reviewed by Fotuhi et al., 2009[29]

Study	Subjects	Exposure	Outcome	Results
Heude et al., 2003[248]	245 men	Erythrocyte membrane lipid composition (total omega-3 PUFA, omega-3: omega-6 fatty acid ratio and DHA:AA ratio	Cognitive decline measured as ≥ 2-point drop in MMSE scores	Higher proportions of omega-3 fatty acid levels in blood were associated with less cognitive decline. Total omega-3 PUFA: OR 0.59 (95% CI 0.38 to 0.93); Omega-3:omega-6 fatty acid ratio: OR 0.55 (0.33 to 0.91) DHA:AA ratio: OR 0.57 (0.35 to 0.92)
Morris et al., 2005[246]	3718 participants	Fish meals per week (0, 1, 2)	Change in global cognitive decline estimated from mixed models	Rate of annual decline decreased by 10 to 13% among individuals who consumed one or more fish meals weekly
Van Gelder et al., 2007[247]	210 men	Fish consumption; DHA and EPA estimated from fish and other foods	Cognitive decline by MMSE	A linear trend was seen between high intake of EPA plus DHA and reduced 5-year cognitive decline (p = 0.01)

Abbreviations: AA=arachidonic acid; CI = confidence interval; DHA= docosahexanenoic acid; EPA = eicosapentaenoic acid; MMSE = Mini-Mental State Examination; OR = odds ratio; PUFA = polyunsaturated fatty acid

Our search identified two additional studies (described in three publications) examining the relationship between omega-3 fatty acids and cognitive decline.[249-251] The study characteristics are summarized in Table 40. Both studies enrolled participants with a mean age < 65 and thus were not included in the review by Fotuhi et al.[29] Beydoun et al. reported results from dietary assessment[250] and plasma omega-3 fatty acids[249] separately. Participants drawn from four U.S. communities (n = 7814) were followed for 6 years; outcomes were reported as reliable change index for three tests. Adjusted analyses showed that higher long chain omega-3 fatty acid intake was associated with less risk of decline as assessed by the delayed word recall and verbal fluency (controlled oral word association) tests, but not as assessed by the digit symbol substitution test or global cognition. An analysis of the 2251 participants with plasma omega-3 fatty acid measurements showed that higher total n-6 PUFAs decreased the risk of global cognitive decline. Total omega-3 PUFAs (OR 0.84; 95 percent CI 0.66 to 1.05), EPA, and DHA were not associated with risk of global cognitive decline. Consistent with the analysis by dietary history, higher levels of DHA and EPA were associated with less decline in verbal fluency.

The second study[251] was a secondary analysis from a 3-year RCT of folic acid in 404 subjects with elevated homocysteine levels. Total omega-3 fatty acid was measured at baseline. Cognitive change was measured with five tests evaluating memory, processing speed, word fluency, sensorimotor speed, and complex speed. Higher plasma omega-3 PUFAs were associated with less decline in sensorimotor speed ($p = 0.02$) and complex speed ($p < 0.01$), but not memory, information processing speed, or word fluency.

Table 40. Omega-3 fatty acids and risk of cognitive decline – recent cohort studies

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Beydoun et al., 2007[249] (subsample from Beydoun et al., 2008[250])	Community (2251) Mean age 56 to 57	6 years	Total plasma n-3 fatty acids; EPA; DHA	Reliable change index for 3 tests: COWA, DSST and delayed word recall tests	Age Sex Education Smoking Alcohol use Caffeine use Physical activity index BMI Dietary factors Baseline cognition	Higher total n-6 PUFAs (OR 0.55, 95% CI 0.37 to 0.81) decreased risk of global cognitive decline Neither total n-3 PUFAs (OR 0.84, 95% CI 0.66 to 1.05), nor EPA, nor DHA decreased risk of global cognitive decline Greater DHA and EPA were associated with less decline on verbal fluency
Beydoun et al., 2008[250]	Community (7814) Mean age 57	6 years	Dietary assessment of n-3 fatty acid intake; analyzed as percentage of energy intake and ratios of fatty acids	Reliable change index for 3 tests: COWA, DSST and delayed word recall tests	Age Race Sex Education Baseline cognition APOE Behavioral factors Nutritional factors HTN	Higher long-chain n-3 fatty acid intake associated with less risk of decline on DWR (OR 0.90, 95% CI 0.81 to 1.00) and COWA (OR 0.85, 0.75 to 0.96), but not DSST or global cognitive decline; no association after adjustment for error in exposure measurement
Dullemeijer et al., 2007[251]	Cohort drawn from RCT of folic acid (404) Mean age 60	3 years	Total plasma n-3 fatty acids	Change on 5 cognitive tests evaluating: memory, processing speed, word fluency, sensorimotor speed and complex speed	Age Sex Education Baseline cognition Erythrocyte folate Alcohol use	Higher plasma n-3 PUFAs associated with less decline in sensorimotor speed ($p = 0.02$) and complex speed ($p < 0.01$) but not memory, information processing speed or word fluency

Abbreviations: APOE = apolipoprotein E gene; BMI = body mass index; CI = confidence interval; COWA = Controlled Oral Word Association; DHA = docosahexaenoic acid; DSST = Digit Symbol Substitution Test; DWR = delayed word recall test; EPA = eicosapentaenoic acid; HR = hazard ratio; HTN = hypertension; OR = odds ratio; PUFA(s) = polyunsaturated fatty acid(s); RCT = randomized controlled trial; RR = relative risk; SD = standard deviation

In summary, the effects of n-3 fatty acids on cognitive decline have been evaluated in five prospective longitudinal studies. Studies vary substantially in measurement of n-3 fatty acids, participant characteristics and outcome measures. Each study reports a positive association between at least one measure of PUFAs and a measure of cognition. However, some results are conflicting. Heude et al.[248] found that higher total omega-3 PUFA and higher omega-3:omega-6 fatty acid ratios were associated with less risk of cognitive decline, while Beydoun et al.[249] found that higher n-6 PUFAs but not total plasma n-3 PUFAS reduced cognitive decline. Another analysis by Beydoun et al.[250] found that higher plasma DHA and EPA were associated with less decline in verbal fluency, but had no effect on global cognition, while Dullemeijer et al.[251] found no association between plasma n-3 PUFAs and verbal fluency but positive effects on sensorimotor and complex speed. Some studies compared multiple measures of exposure with multiple measures of cognition, increasing the risk for detecting spurious associations. The positive results could be explained by residual confounding. Eating fish might be a proxy for individuals with healthier lifestyles than those who do not eat fish and effects on cognitive decline might have little to do with fish consumption. Despite these cautions, these studies support the possible association between higher consumption of PUFAs and less cognitive decline.

Other fats. We identified one eligible cohort study that examined the association between cognitive decline and fat intake.[252] The study is summarized in Table 41; a detailed evidence table is provided in Appendix B. The study used a community sample in the United States. Participants were non-demented at baseline. The median length of followup was 5.6 years. The study used sample selection methods to minimize selection bias. It used self-reported information to estimate fat intake. Based on a validation substudy, the authors reported the Pearson correlations for comparative validity with 24-hour dietary recalls were 0.40 for monounsaturated fat, 0.47 for saturated fat, 0.36 for polyunsaturated fat, and 0.39 for cholesterol. The study compared baseline characteristics between those exposed and unexposed. The case definitions for the studies are described in Table 41. The analyses appear appropriate and were controlled for relevant potential confounders. The study did not conduct a priori sample size calculations.

The study showed that higher intake of saturated fats and trans-unsaturated fats were linearly associated with greater cognitive decline. But total fat, vegetable and animal fat, and cholesterol were not associated with cognitive change over time. In another study on this same sample,[253] the authors noted an interaction between copper intake and fat intake in that higher copper intake was associated with greater cognitive decline in subjects with high saturated and trans fats intake.

In conclusion, there is a single study each addressing risk of AD and risk of cognitive decline associated with dietary fat intake. The two studies provide preliminary evidence for a deleterious association between increased saturated fat and trans fat intake and risk of AD or cognitive decline. Further research is needed both to validate self-report exposure measures of dietary intake and also to confirm the findings in the present study.

Table 41. Intake of various types of fat and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Morris et al., 2004[252]	Community cohort (2560)	5.6 years	Estimates of total intake of various types of fat during the previous year were calculated from self-report responses on a modified Harvard food frequency questionnaire	Cognitive decline on standardized composite measure from all tests	Age Race Sex Educational level Total energy from calories Smoking Alcohol use Time between assessments HTN Vitamin C Vitamin E	Higher intake of saturated fat (trend p = 0.04) and trans-unsaturated fat (trend p = 0.07) were linearly associated with greater decline in cognitive score over 6 years. When excluding individuals who changed pattern of fat intake in last 10 years and/or those scoring in lowest 15%, effect became stronger. Total fat, vegetable and animal fat, and cholesterol not associated with cognitive change

Abbreviation: HTN = hypertension

Trace metals. We did not identify any systematic reviews evaluating the association between trace metals and cognitive decline. Our search identified three primary research publications[245,253,254] from two cohort studies.

Selenium. Selenium is an antioxidant and constituent of brain selenoproteins that may be important for the maintenance of brain functions. The association between plasma selenium and cognitive change was described in two publications from the same community-based cohort conducted in older adults with normal cognition from the Nantes district of France.[245,254] These publications are summarized in Table 42; detailed evidence tables are provided in Appendix B. Subjects were recruited in part from advertisement campaigns that may introduce selection bias. It is assumed here that the majority of participants were non-demented at baseline based on the relatively young age at baseline for both studies and the lengthy followup period in one of the studies.[254] Followup rates were 84 percent at 4 years and 54 percent at 9 years. Analyses were adjusted for multiple potential confounding variables. Berr et al.[245] described the relationship between baseline selenium levels and at least a 3-point decline on the MMSE at 4 years. Selenium levels below the 25th percentile increased the risk for cognitive decline (OR 1.58; 95 percent CI 1.08 to 2.31). Akbaraly et al.[254] reported the association between change in plasma selenium levels and declines on four cognitive measures. Analyses were conducted to examine the 2- and 9-year change in selenium with the four cognitive measures, evaluating change in cognition as both a continuous measure and as a dichotomous variable using two separate thresholds. Analyses were not adjusted for multiple comparisons. Two-year change in plasma selenium was not associated with change in cognition. When change in cognition was analyzed as a continuous variable, the 9-year change in selenium was associated only with the MMSE. When cognition was analyzed as a dichotomous variable (10th or 25th percentile of decline), change in plasma selenium was associated with declines in the finger tapping test. Associations with other cognitive measures were inconsistent depending on the threshold for cognitive decline.

In summary, the results of one of these studies provide limited support for a possible association between baseline selenium and cognitive decline. However, a number of issues raise concerns about the robustness of this finding, namely: the potential selectivity of the sample, the lack of an association with change in selenium level and cognitive change, and the modest effect size that may indicate confounding due to other factors.

Table 42. Plasma selenium levels and risk of cognitive decline*

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Berr et al., 2000[245]	Community cohort (1389)	4 years	Plasma selenium	MMSE decline of ≥ 3 points	Age Sex Educational level Baseline cognitive status Depressive symptoms Alcohol and tobacco use BMI Cholesterol/ triglycerides	Low selenium (<25th percentile) increased risk of cognitive decline (OR 1.58; 95% CI 1.08 to 2.31); no dose-response relationship
Akbaraly et al., 2007[254]	Community cohort (1228)	9 years	Long-term (9-year) and short-term (2-year) change in plasma selenium	Decline on the MMSE, Trails B, DSST, and FTT using two thresholds: 10th and 25th percentiles of change	Sex Educational level Time period of observation Baseline plasma selenium Diabetes Hypertension Hyperlipidemia History of cardiovascular disease	Short-term selenium change was not associated with cognitive change at 2, 4, 6, or 9 years Long-term selenium decrease was associated with MMSE decline at 9 years (beta = 0.38; 95% CI 0.14 to 0.62), but not other cognitive measures

* The two publications summarized here are based on the same patient cohort.
Abbreviations: DSST = Digit Symbol Substitution Test; FTT = Finger Tapping Test; MMSE = Mini-Mental State Examination; Trails B = Trail Making Test Part B

Copper, zinc, and iron. A single cohort study involving 3718 older adults from a community sample in Chicago, Illinois, evaluated the relationship between dietary copper, zinc, and iron and cognitive decline.[253] This study is summarized in Table 43; a detailed evidence table is provided in Appendix B. Subjects were non-demented at baseline, and were followed for a median of 5.5 years; 88 percent of survivors completed followup. Copper, zinc, and iron intake was estimated based on the modified Harvard Food Frequency Questionnaire. Based on a validation analyses in a subsample, the authors reported that Pearson correlations between total intake levels on the questionnaire and multiple 24-hour dietary recalls were 0.46 for copper, 0.50 for zinc, and 0.43 for iron. Cognitive decline was measured as the standardized composite of four tests. Analysis adjusted for multiple potential confounding variables including other nutritional factors (vitamins C and E, niacin, folate) showed no association between copper, zinc, or iron and cognitive decline. A power calculation was not reported. However, higher copper intake was associated with greater cognitive decline in subjects with high saturated and trans fats (difference in cognitive decline for highest versus lowest copper quintile was -0.61 standardized units/year, $p < 0.01$). This interaction between copper intake and saturated fat intake was specified a priori, supported by an animal study showing that neurodegenerative changes may be exacerbated by consumption of trace amounts of copper in drinking water. These results provide preliminary evidence that high copper intake may be associated with more rapid cognitive decline in individuals who consume a diet high in saturated and trans fats.

Table 43. Intake of copper, zinc, and iron and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Morris et al., 2006[253]	Community cohort (3718)	Median 5.5 years	Copper, zinc, iron intake estimated from HFFQ	Standardized composite of 4 tests: East Boston immediate and delayed recall tests, MMSE, Symbol Digit Modalities Test	Age Race Sex Educational level Cognitive activities Physical activities Alcohol use Stroke Heart disease HTN DM Vitamins C and E, niacin, and folate	No association between copper, zinc or iron and cognitive decline. In subgroup with high saturated and trans fat, higher copper intake was associated with greater cognitive decline

Abbreviations: DM = diabetes mellitus; HFFQ = Harvard Food Frequency Questionnaire; HTN = hypertension; MMSE = Mini-Mental State Examination

Mediterranean diet. We identified two eligible cohort studies that examined the association between cognitive decline and the Mediterranean diet.[86,87] The Mediterranean diet is characterized by high intake of vegetables, legumes, fruits, and cereals; high intake of unsaturated fatty acids (mostly in the form of olive oil), but low intake of saturated fatty acids; a moderately high intake of fish; a low-to-moderate intake of dairy products (mostly cheese or yogurt); a low intake of meat and poultry; and a regular but moderate amount of alcohol, primarily in the form of wine and generally during meals. The included studies are summarized in Table 44; detailed evidence tables are provided in Appendix B. One study[87] used a community sample in Europe, and the other study[86] used a community sample in the United States. Participants were cognitively normal at baseline in one study[86] and non-demented in the other study.[87] The outcome for one study was progression to MCI; the diagnosis for MCI was retrospectively assigned.[86] In the other study, the outcome was longitudinal change on multiple cognitive tests. Length of followup ranged from an average of 4.5 to 7 years. Exposure was determined based on self-reported information from a semi-quantitative food frequency questionnaire. Both studies used similar methods to calculate a Mediterranean diet score based on the responses on this questionnaire. The investigators of both studies noted that they had previously reported that this questionnaire has adequate validity and reliability based on substudies of segments of the questionnaire. Both studies used sample selection methods to minimize selection bias and compared baseline characteristics by exposure level. One study stated that the outcome diagnosis was assigned blind to the exposure level;[86] it is assumed here that in the other study that the cognitive measures were administered blind to exposure level.[87] Analyses were appropriate and controlled for relevant potential confounders. Neither study conducted a priori sample size calculations.

Scarmeas and colleagues[86] reported that compared to those with the lowest tertile Mediterranean diet score, those in the middle tertile were not at significantly lower risk of developing MCI (HR 0.83; 95 percent CI 0.62 to 1.12), but being in the the highest tertile was associated with lower risk of MCI (HR 0.72; 95 percent CI 0.52 to 1.00). The hazard ratio for the trend was also significant (HR 0.85; 95 percent CI, 0.72 to 1.00; P for trend = 0.05). Feart and colleagues[87] found a significant association between a higher Mediterranean diet score and fewer MMSE errors (β = -0.006; 95 percent CI, -0.01 to -0.0003; P = 0.04 for 1 point of the Mediterranean diet score), indicating less decline on the MMSE over 5 years. Longitudinal performance on other cognitive tests did not show this association, except when participants with incident dementia were excluded. In this latter analysis, the memory test showed slightly less decline associated with a higher Mediterranean diet score (β = 0.05; 95 percent CI 0.005 to 0.010; P = 0.03 for 1 point of the Mediterranean diet score).

In summary, there is preliminary evidence that greater adherence to a Mediterranean diet may be associated with less cognitive decline in later life. Some caution is warranted in drawing conclusions from these findings due to the small effect sizes, minimally significant results, and the fact that the association is limited to few of the multiple cognitive measures. Confirmation of the findings is needed.

Table 44. Mediterranean diet and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Scarmeas, et al., 2009[86]	Community cohort (1875)	Mean 4.5 (2.7) years 275 incident MCI cases	Self-reported responses on a food frequency questionnaire	NINCDS-ADRDA DSM MCI criteria applied currently accepted diagnostic criteria to previously collected data	Age Race Sex Education APOE BMI Interval between dietary assessment and cognitive assessment	Higher adherence to Mediterranean diet associated with lower risk of progression from cognitively normal to MCI Using lowest tertile of adherence as reference: Middle tertile: HR 0.83 (95% CI 0.62 to 1.12) Highest tertile: HR 0.72 (0.52 to 1.00) Trend: HR 0.85 (0.72 to 1.00; P for trend = 0.05)
Feart et al., 2009[87]	Community cohort (1410)	7 years	Self-reported responses on a food frequency questionnaire	Longitudinal change on the four cognitive tests: MMSE, Isaacs Set Test , Benton Visual Retention Test , and Free and Cued Selective Reminding Test	Age Sex Education Marital Status Energy Intake Physical Activity Depression symptoms Taking 5 medications or more APOE Cardiovascular risk factors Stroke	Higher Mediterranean diet score associated with fewer MMSE errors (β = -0.006; 95%CI -0.01 to -0.0003; P = 0.04 for 1 point of the Mediterranean diet score) and therefore slower MMSE cognitive decline. Longitudinal performance on other cognitive tests did not show this association. Among the subgroup who did not develop dementia, higher Mediterranean diet score associated with fewer MMSE errors (β = -0.006; 95% CI -0.011 to -0.007; P = 0.03 over 5 years for 1 point of the Mediterranean diet score) and less decline on the memory test (β = 0.05; 95% CI 0.005 to 0.010; P = 0.03)

Abbreviations: APOE = apolipoprotein E gene; BMI = body mass index; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; HR = hazard ratio; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association

Intake of fruit and vegetables. We identified two eligible cohort studies that examined the association between cognitive decline and intake of fruits and vegetables.[255,256] The outcomes of both studies were continuous variables. The two studies are summarized in Table 45; detailed evidence tables for the studies are in Appendix B. Both studies used community samples in the United States. One study stated the participants were non-demented at baseline;[256] the other study[255] did not provide information about baseline cognitive level, but it is assumed here that most of the participants were non-demented at baseline. The length of followup ranged from 2 to 5.5 years. Both studies used sample selection methods to minimize selection bias. Both studies used self-reported information to estimate fruit and vegetable intake, and both reported additional substudies aimed at validating the food frequency questionnaires. For the foods of interest in these analyses, the correlations tended to be in the moderate range for responses on the food frequency questionnaires and more detailed nutrition data. Both studies compared baseline characteristics between those exposed and unexposed. The case definitions for the studies are described in Table 45. The analyses appear generally appropriate and were controlled for relevant potential confounders. Neither study conducted a priori sample size calculations.

Both studies reported a significant protective association between higher amounts of vegetables and lower rates of cognitive decline, with the association being the strongest for green leafy vegetables. There were no significant associations between amount of fruit intake and cognitive decline. The results from these two studies are consistent in suggesting a protective effect on cognition associated with eating vegetables, but the actual difference in mean scores between the groups is quite small. Additional studies confirming these findings would be useful to rule out the possibility of residual confounding explaining the results and to determine whether these small differences have clinical significance.

Table 45. Intake of fruit and vegetables and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Kang et al., 2005[255]	Community cohort (13,338)	2 years	Fruit and vegetable intake estimated from self-reported responses on food frequency questionnaire administered every 2 years for up to 5 time points	Decline on cognitive measures	Age Education High blood pressure High cholesterol Diabetes Coronary heart disease Hormone therapy Age at menopause, BMI Smoking Antidepressant use NSAID use Alcohol intake Physical activity Total energy intake Mental health and vitality indices Vitamin supplementation	On global cognitive score: Highest quintile of vegetable intake showed less decline than the lowest quintile (mean difference 0.04 (p trend < 0.01) Highest quintile of green leafy vegetables showed less decline than lowest quintile (mean difference 0.05; p trend < 0.001) Highest quintile of legumes showed less decline than lowest quintile (mean difference 0.03; p trend 0.02) No differences in cognitive decline associated with fruit intake Results for performance on a verbal memory test and on the TICS were similar to those for the global cognitive score
Morris et al., 2006[256]	Community cohort (3718)	Median 5.5 years	Estimates of total intake of fruits and vegetables during the previous year were calculated from self-report responses on a modified Harvard food frequency questionnaire. Categorized by quintiles, range 0.8 to 4.1 servings per day of vegetables and 0.6 to 3.9 servings per /day of fruits.	Cognitive decline on standardized composite measure from all tests	Age Race Sex Educational level Cognitive activities Physical activities Alcohol use	Higher intake of vegetables associated with less cognitive decline (trend p = 0.04). Higher intake of fruit not associated with rate of cognitive decline (trend p = 0.55) High intake of green leafy vegetables showed strongest association with reduction in cognitive decline (trend p = 0.03)

Abbreviations: BMI = body mass index; NSAID = non-steroidal anti-inflammatory drug; TICS = Telephone Interview for Cognitive Status

Total intake of calories, carbohydrates, fats, and proteins. We identified no systematic reviews or studies evaluating total intake of calories, carbohydrates, fats, and protein and risk of cognitive decline.

Medical Factors

Vascular factors. Factors considered under this heading include diabetes mellitus, metabolic syndrome, hypertension, hyperlipidemia, and homocysteine.

Diabetes mellitus. We identified two systematic reviews that examined the relationship between diabetes mellitus and risk of cognitive decline.[42,43] Lu et al.[42] identified seven prospective, longitudinal cohort studies published between 1999 and November 2007 involving 38,573 subjects. Five studies were conducted in the United States and two in Western Europe. Ascertainment of diabetes varied among studies, with the diagnosis of diabetes based on history, medical records, fasting glucose, or oral glucose tolerance test. Heterogeneity between studies was assessed using the chi-square test, and publication bias was examined using visual inspection of funnel plots and Egger's test. No heterogeneity or publication bias was found. Global measures of cognitive function included the MMSE, the 3MS, and the TICS. Several studies also examined executive function using Trail Making Test Part B (Trails B), verbal fluency, and Digit Symbol Substitution Test (DSST). Individuals with diabetes mellitus were found to have faster decline in global cognitive function as measured by change in MMSE, 3MS, or TICS score after 2 to 7 years of followup. Similarly, baseline diabetes mellitus was also associated with a faster decline in measures of executive function.

An earlier systematic review by Cukierman et al.[43] reported that the annual rate of change in MMSE or 3MS scores in three studies was 1.2 to 1.5 times faster in diabetic subjects than in non-diabetics. This review also examined studies that assessed global cognitive change as a categorical variable. Cognitive decline was defined as either a percent reduction from baseline scores, or reduction below a particular threshold (for example, a score less than 80 percent of the population). Diabetics were more likely than non-diabetic subjects to experience a decline in MMSE or 3MS score of ≥ 6.6 to 11.5 percent from their baseline score (ORs ranged from 0.7 to 1.7 in four studies), or to score in the bottom 15 or 20 percentile of the population (ORs ranged from 1.0 to 1.2 in two studies), but only one of these six studies had a lower 95 percent CI that exceeded 1.0. A meta-analysis of the results from six studies that performed the MMSE at baseline and followup found that the OR for cognitive decline for diabetics as measured by the MMSE was 1.2 (95 percent CI 1.05 to1.4). There was no statistical evidence of heterogeneity (chi squared = 6.73, df = 5 (p = 0.24); I^2 = 25.7 percent). A similar analysis for the DSST (two studies) found that diabetics were more likely to decline by at least 7.3 percent from their baseline score (OR 1.6; 95 percent CI 1.2 to 2.2), or to score in the bottom 15 percentile of the population than were non-diabetics (OR 2.3; 95 percent CI 1.2 to 4.3). A meta-analysis of the two studies that performed the DSST found that diabetic subjects were at increased risk of a decline in performance compared to non-diabetics (OR 1.7; 95 percent CI 1.3 to 2.3). Six studies used a composite of other measures of cognitive performance to detect cognitive decline. Five of these found that subjects with diabetes had a higher risk of cognitive decline than non-diabetics. In three of the studies that demonstrated decline, the lower limit of the 95 percent CI exceeded 1.0. Cukierman et al.[43] concluded that people with diabetes have a greater risk and rate of cognitive decline than people without diabetes.

We identified five additional studies on the association between diabetes mellitus and cognitive decline.[257-261] These studies are summarized in Table 46; detailed evidence tables are provided in Appendix B. One study was from Australia,[257] one from Europe,[259] and three from the United States.[258,260,261] The total number of subjects enrolled was 9056; 58.2 percent were women. Only two studies had a significant number of African-American subjects. The mean age of subjects ranged from 59 to 74 years, and the duration of studies was 4 to 14 years. One study examined conversion to a diagnosis of MCI or any form of MCI (Age Associated Memory Impairment, Age Associated Cognitive Decline; Mild Neurocognitive Disorder, CDR = 0.5 and Other Cogntive Disorder) and found no association between diabetes and cognitive impairment.[257] Yaffe et al. did not use a categorical diagnosis, but divided subjects ranging in age from 70 to 79 years into three groups based on performance on the 100-point Modified Mini-Mental State Examination (3MS).[258] Subjects whose 3MS scores were stable at baseline, 3, 5, and 8 years (slope of scores ≥ 0) were called cognitive maintainers, those with slopes between 0 and > 1 SD below mean were called minor decliners, and those with slope that declined by more than 1 SD were major decliners. Thirty percent of the population maintained cognitive function over 8 years, 53 percent demonstrated minor decline, and 16 percent had major cognitive decline. The investigators reported that in multivariate analysis, diabetes mellitus was not significantly associated with being either a minor or major decliner in cognitive function.[258] Comijs et al. used the 30-point MMSE as a measure of general cognitive function in a 6-year study of 1358 subjects ranging in age from 62 to 85 years.[259] Using a Generalized Estimated Equation (GEE) model, investigators found that subjects with diabetes had a significantly lower baseline MMSE score, but cognitive change over time was not significantly different from non-diabetics. Diabetes was also associated with lower baseline scores on Raven's Colored Progressive Matrices, the Alphabet Coding Task-15, and the Dutch version of the Auditory Verbal Learning Test (AVLT), but cognitive decline over time was only significant for delayed recall on the AVLT ($p < 0.01$). Knopman et al. examined the association of diabetes mellitus with cognitive decline over 14 years using three neurocognitive tests (Digit Symbol Substitution [DSST], Delayed Word Recall [DWR] and Word Fluency [WF]).[260] Although there was a decline in all three measures in subjects with diabetes, it was significant in multivariate analysis only for WF ($P = 0.021$). In univariate analysis adjusted for race, age, sex, and education, subjects with diabetes had a greater average annual decline on DSST ($P = 0.002$) and WF ($P = 0.003$), but not DWR. Investigators found no interaction between risk factors. Carmelli et al examined the effect of APOE e4 genotype on 10-year cognitive decline in 410 subjects with midlife hyperglycemia.[262] Investigators found that APOE e4 carriers with midlife hyperglycemia experienced greater decline than APOE e4 carriers without hyperglycemia and hyperglycemic subjects who did not carry and e4 allele.

In summary, the data linking diabetes mellitus with a rapid rate of cognitive decline are mixed, with most studies showing a modest association. A number of studies have identified declines in selective cognitive function (e.g., DSST, WF and delayed recall on AVLT) in diabetics, but the specific domain affected has varied across studies. Possible explanations for variation in results include use of different criteria to diagnose diabetes mellitus, and failure to consider the effect of duration and severity of diabetes on cognitive outcome. More data are needed on the effect of various forms of diabetes treatment (insulin versus oral agents versus diet) and the role of comorbid vascular factors and hyperinsulinemia on cognitive decline.

Table 46. Diabetes mellitus and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Cherbuin et al., 2009[257]	Community cohort (2082) Baseline Age 60-64	4 years 18 cases MCI at 4 years; 64 cases any mild cognitive disorder	Diabetes mellitus (self-report and diabetic medications recorded)	Incident MCI or any mild cognitive disorder (age-associated memory impairment, age-associated cognitive decline, mild neurocognitive disorder)	Age Race Education	OR (95% CI): Diabetes converting to MCI: 0.73 (0.95 to 5.52); p = 0.756 Diabetes converting to any mild cognitive disorder: 2.06 (0.99 to 4.28); p = 0.054
Yaffe et al., 2009[258]	Community cohort (2509) Baseline Age 70-79	8 years 30% maintainers 53% minor decline 16% major decline	Diabetes mellitus (self-report, direct measurement glucose [fasting > 126 mg/dL or 2-hour challenge > 200 mg/dL], and use of diabetic medications)	Comparison of scores on 3MS at baseline, 3, 5, and 8 years. Slope of scores < 0 = maintainers; slope between 0 and > 1 SD below mean = minor decliners; and slope > 1 SD below mean = major decliners	Age Race Education APOE genotype	OR (95% CI) for diabetics: Maintainer vs. minor decliner: 0.91 (0.64 to 1.30) Minor vs. major decliner: 1.35 (0.92 to 2.00)
Comijs et al., 2009[259]	Community cohort (1358 with complete data)	6 years	Diabetes mellitus (self-report)	General cognitive function (MMSE) Fluid intelligence (Raven's Colored Progressive Matrices) Processing speed (Alphabet Coding Task) Auditory Verbal Learning Test	Age Sex Educational level Presence of comorbid disease outside of the 7 of interest Smoking Alcohol use Antidepressant Benzodiazepines Depressive symptoms (CES-D) Impaired vision, hearing or mobility (6 typical ADLs assessed)	GEE model (coefficients *B*, with 95% CIs): General cognitive function over time: Negatively affected by DM (-0.49; -0.86 to -0.11) Fluid intelligence over time: Negatively affected by DM (-1.03; -1.54 to -0.51) Information processing speed over time: Negatively affected by DM (-0.76; -1.53 to 0.00) Memory performance (immediate and delayed recall) over time: Immediate: Negatively affected by DM (-0.44; -0.83 to -0.06) Delayed: Negatively affected by DM (-0.65; -0.95 to -0.17)
Knopman	Community	14 years	Diabetes mellitus	DSST	Age	Difference in average baseline cognitive

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
et al., 2009[260]	cohort (1130)		(fasting glucose > 126 mg/dL, non-fasting glucose > 200 dL, self-reported history of diabetes, or treatment for diabetes in previous 2 weeks)	DWR WF	Race Sex Educational level Vascular factors Time Risk factor x time interaction	test scores (P value): <u>Diabetes</u> DSST: 0.25 (0.803) DWR: -0.19 (0.173) WF: 0.60 (0.597)
Carmelli et al., 1998[262]	Community cohort (NHLBI WWII twin substudy) (410)	10 to 25 years	Midlife hyperglycemia (1-hour post-prandial glucose > 200 mg/dL or use of hypoglycemic agent or insulin) APOE genotype	Change in test scores: MMSE, DSST, BVRT	Age Race Sex Baseline score Incident cardiovascular disease	Mean change (SD): APOE e4+ and hyperglycemia present: MMSE: 1.66 (.39) DSST: 7.84 (1.08) BVRT: 1.05 (0.26) APOEe4+ and hyperglycemia absent: MMSE: 0.73 (.28) DSST: 4.47 (.76) BVRT: 0.53 (0.19) APOE e4- and hyperglycemia present: MMSE: 0.47 (0.2) DSST: 4.14 (0.56) BVRT: 0.84 (0.14) APOEe4- and hyperglycemia absent: MMSE: 0.47 (0.16) DSST: 3.34 (0.45) BVRT: 0.37 (0.11) All scores are significantly different from 0 and statistically significant at $p < 0.05$

Abbreviations: 3MS = Modified Mini-Mental State Examination; ADLs = activities of daily living; APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; BVRT = Benton Visual Retention Test; CES-D = Venter for Epidemiologic Studies Depression scale; CI = confidence interval; DM = diabetes mellitus; DSST = Digit Symbol Substitution Test; DWR = delayed word recall; GEE = generalized estimated equations; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; OR = odds ratio; SD = standard deviation; WF = Word Fluency Test

Metabolic syndrome. We identified four prospective, longitudinal cohort studies, involving 5713 subjects, that evaluated the association between metabolic syndrome and cognitive impairment.[260,263-265] These studies are summarized in Table 47; detailed evidence tables are provided in Appendix B. One study was conducted in the Netherlands, one in Singapore, and two in the United States; all were community samples. Metabolic syndrome was identified in three studies using National Cholesterol Education Program 3rd Adult Treatment Panel Guidelines (NCEP-ATPIII),[260,263,264] and in the other using International Diabetic Federation criteria.[265] The NCEP-ATPIII criteria require at least three of the following for a diagnosis of metabolic syndrome:

1) Waist measurement > 88 cm for women or > 102 cm for men.
2) Hypertriglyceridemia (≥ 150 mg/dL [≥ 1.69 mmol/L]).
3) Low HDL (men < 40 mg/dL [< 1.03 mmol/L]); women < 50 mg/dL [< 1.29 mmol/L]).
4) High blood pressure (systolic ≥ 130 mmHg; diastolic ≥ 85 mmHg) or currently using an antihypertensive medication.
5) High fasting glucose (≥ 110 mg/dL [≥ 6.10 mmol/L]) or currently using anti-diabetic medication (insulin or oral agents).

The International Diabetes Federation criteria are similar, but require a waist circumference greater than 90 cm for men (> 80 cm for women) plus at least two of the following: elevated blood pressure or use of antihypertensive medication; elevated fasting glucose (≥ 5.6 mmol/L) or use of antidiabetic drugs; elevated triglycerides (1.7 mmol/L) or use of lipid-lowering agents; or low HDL cholesterol (< 0.9mmol/L in men and < 1.1mmol/L in women) or use of lipid-lowering agents.

The definition of cognitive change also differed among the studies. Yaffe et al.[263] described cognitive change as a decline of 5 or more points in the 100-point Modified Mental Status (3MS) examination at either the 3- or 5-year evaluation, while Ho et al.[265] defined change as a 2-point decline on the 30-point MMSE over 1 to 2 years. Van den Berg et al.[264] and Knopman et al.[260] examined the effect of metabolic syndrome on the rate of change in a battery of tests over 5 years of followup. Van den Berg et al. used the MMSE, Stroop, Letter digit coding, and word list immediate learning or delayed recall, and Knopman et al. used Digit Symbol Substitution, Delayed Word Recall and Word Fluency. There were also several differences among the study populations. Van den Berg et al.[264] examined residents of Leiden, The Netherlands, who were 85 or older, and 17 percent of the participants had MMSE scores ≤ 18 at baseline. Ho et al.[265] studied people from Singapore with a mean age of approximately 65, and all participants had MMSE scores ≥ 24. Yaffe et al.[263] studied black and white elders from Memphis, Tennessee, and Pittsburgh, Pennsylvania, who ranged in age between 70 and 79 years of age, with a mean baseline 3MS score of 90. This latter study did not describe the number of subjects with low 3MS scores, but required a self-report of normal functioning on activities of daily living and the absence of a diagnosis of dementia to participate. The subjects in the Knopman et al. study[260] were a subset of participants in the Atherosclerosis Risk in Communities (ARIC) study. In all studies, participants with metabolic syndrome were more likely to be women, and in two studies they had lower levels of education; both female sex and low education are associated with an increased risk of AD, so baseline differences in the population may confound interpretation of results. All studies adjusted for important confounders, such as sex and educational level. Yaffe,[263] Ho,[265] and Knopman and colleagues[260] adjusted for age, but van den Berg and

colleagues[264] did not, possibly because of the limited age difference in the latter's study participants. Van den Berg et al. and Knopman et al. also did not stratify results based on baseline cognitive testing. There were also differences in followup: in the study by van den Berg and colleagues, 51 percent of subjects died before repeat cognitive assessment,[264] while followup rates for Ho, Yaffe, and Knopman and colleagues were 64 percent, 89 percent, and 59 percent, respectively,[260,263,265] Mortality in the study by van den Berg et al. was not associated with metabolic syndrome (HR 0.9; 95 percent CI 0.7 to 1.2).

Two studies found that metabolic syndrome was modestly associated with cognitive decline. Yaffe and colleagues reported that 26 percent of participants with metabolic syndrome had a decline of at least 5 points on the 3MS, compared to 21 percent of subjects without metabolic syndrome (adjusted RR 1.20; 95 percent CI 1.02 to 1.41).[263] They further analyzed their data based on whether participants had evidence of increased inflammation as measured by the serum markers C-reactive protein (CRP) and interleukin 6. Subjects with metabolic syndrome and increased inflammatory markers were at greater risk of cognitive decline (adjusted RR 1.66; 95 percent CI 1.19 to 2.32) compared to those with metabolic syndrome and normal levels of inflammatory markers (adjusted RR 1.08; 95 percent CI 0.89 to 1.30), suggesting that inflammation is a mechanistically important mediator of cognitive change in metabolic syndrome. Ho and colleagues reported that subjects with metabolic syndrome were more likely to experience a 2-point decline on the MMSE than subjects without metabolic syndrome: among subjects with metabolic syndrome, 19.9 percent had a 2-point decline, compared to 14 percent of subjects without the syndrome (OR 1.42; 95 percent CI 1.10 to 1.98).[265] Knopman et al. prospectively followed 1130 individuals with a mean age at baseline of 59 years for 14 years.[260] Forty-six percent of the cohort met criteria for metabolic syndrome, and 52 percent were African-American. Investigators reported that subjects with metabolic syndrome had a statistically significant greater annual decline on word fluency than other subjects in univariate testing that controlled for race, age, sex, and education ($P < 0.001$). Metabolic syndrome was not associated with a significant decline on Digit Symbol Substitution or Delayed Word Recall Tests. The authors also reported that there was no evidence of differential effects of risk factors on cognitive decline by race or sex. Van den Berg et al. found that metabolic syndrome was not associated with lower cognitive performance in their study of people over the age of 85 years.[264] In contrast, the Leiden 85-Plus study data showed that subjects with metabolic syndrome had a slower rate of cognitive decline on the MMSE, Stroop, and Letter Digit Coding tests than subjects without metabolic syndrome. The authors suggested that the difference in age between Leiden 85-Plus study participants and participants in the other studies may explain the disparate findings. There is some literature to suggest that weight loss, low blood pressure, and low cholesterol values are associated with an increased risk of dementia and higher mortality in the old-old, which could explain the protective effect of metabolic syndrome in the older group. There may also be a survivor effect, such that individuals who reach 85 despite having metabolic syndrome may be less susceptible to the adverse effects of these risk factors.

In summary, metabolic syndrome is associated with a modestly increased risk of cognitive decline in studies involving subjects under the age of 80. The relationship between metabolic syndrome and risk of cognitive decline may not be valid in persons over the age of 85 years. There is limited evidence that inflammation may mediate some of the risk of metabolic disease in elders under the age of 80, and measures of inflammation should be included in future studies. Future studies should also include various definitions of metabolic syndrome and subjects with

onset of metabolic syndrome in midlife, as syndrome duration may be relevant to late-life cognitive decline and dementia.

Table 47. Metabolic syndrome and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Yaffe et al., 2004[263]	Community cohort (2632)	3 to 5 years	Metabolic syndrome using NCEP-ATPIII criteria (see text, above, for details)	5-point decline in 3MS at 4-year followup	Age Sex Education Race Baseline cognition Smoking	Unadjusted RR 1.21 (95% CI 1.03 to 1.43)
Van den Berg et al., 2007[264]	Community cohort (497)	1 to 5 years	Metabolic syndrome using NCEP-ATPIII criteria (see text, above, for details)	Rate of decline in battery of tests	Sex Level of education	Additional annual effect on: MMSE: 0.18 (SD .07); p = 0.01 Stroop: -1.49 (SD 0.59); p = 0.01 Letter digit coding: 0.26 (SD .09); p = 0.005
Ho et al., 2008[265]	Community cohort (1352)	1 to 2 years	Metabolic syndrome using International Diabetic Federation Guidelines (see text, above, for details)	≥ 2-point decline on MMSE	Age Sex Education Baseline cognitive status Smoking Alcohol use Depression APOE genotype Length of followup	Metabolic syndrome more likely to have 2-point decline on MMSE: 14% vs. 19.9%; p < 0.008 OR for metabolic syndrome: 1.42 (95% CI 1.10 to 1.98); p < 0.008
Knopman et al. 2009[260]	Community cohort (1130)	Median followup 14 years	Metabolic syndrome using NCEP-ATPIII criteria (see text, above, for details)	DSST DWR WF	Age Race Sex Educational level Vascular factors Time Risk factor x time interaction	Difference in annual rate of change for metabolic syndrome: DSST: -0.05 (NS) DWR: 0 WF: -0.12 (p < 0.001)

Abbreviations: 3MS = Modified Mini-Mental State Examination; APOE = apolipoprotein E gene; CI = confidence interval; DSST = Digit Symbol Substitution Test; DWR = delayed word recall; MMSE = Mini-Mental State Examination; NCEP-ATPIII = National Cholesterol Education Program 3rd Adult Treatment Panel Guideline; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; NS = not statistically significant; OR = odds ratio; RR = relative risk; SD = standard deviation; WF = Word Fluency Test

Hypertension. We did not identify any good quality systematic reviews evaluating hypertension and risk of cognitive decline. Our own search identified 16 unique cohorts described in 19 publications that examined the association between hypertension and cognitive decline.[108,163,258,260,262,266-280] These studies are summarized in Table 48; detailed evidence tables are provided in Appendix B. The included studies involved more than 43,000 subjects. Studies were widely heterogeneous. Three studies[266-268] assigned diagnoses of incident MCI using different modifications of Petersen's criteria. The other studies looked at changes in cognitive test scores over time. Twelve studies[108,163,258,260,262,271,272,274-276,279,280] used community cohorts from the United States, and one used a community cohort from France.[278] More narrowly defined community-based cohorts included those made up of WWII twin pairs,[262,272] retired Catholic clergy,[108] and a cohort drawn from the participants in the Study of Osteoporotic Fractures.[271] Two publications described observational analyses based on RCTs. One cohort[273] was formed by the subjects (aged ≥ 60 years) from the Systolic Hypertension in the Elderly Program (SHEP) trial, a study of anti-hypertension treatment in which all subjects had a SBP > 160 and a DBP < 90 and lacked "clinically obvious dementia" at baseline. Another cohort[277] used subjects from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, a test of cognitive training. Subjects (mean age ~ 74 at baseline) in ACTIVE had MMSE scores > 22 and were not functionally impaired. Subjects with controlled hypertension would have been classified as normotensive, and analyses were not adjusted for antihypertensive medication use.

The studies also used varying definitions of hypertension, as noted in Table 48. Some studies treated blood pressure as a continuous variable.[108,275,279] Others used self-reported hypertension as one component of designating a subject as hypertensive or as the sole means of determining the presence of hypertension.[163,258,271,276] In the cohort from the SHEP trial,[277] all participants had isolated systolic hypertension. Definitions of hypertension were set a priori in some cases,[258,260,266,273,276,277] and were clearly based on the data in another.[274] In the remainder of the studies, hypertension was self-reported, treated as a continuous variable, or not clearly defined a priori.

There were 2990 subjects in the studies that diagnosed MCI. Rates of incident MCI varied. Solfrizzi and colleagues[266] describe 113 cases of incident MCI in a population of 1524 over 3.5 years. Tervo et al.[267] found 65 cases of incident MCI in a study sample of 548 over 3.26 years. Reitz and colleagues[268] found 334 cases of incident MCI in a study sample of 918 over 4.7 years. No significant association between hypertension and MCI was found in any of these studies.

Studies from community samples that evaluated the effects of hypertension on various cognitive tests[108,163,258,260,262,271,272,274-276,278-280] had mixed results. For various cognitive domains, associations between hypertension and cognitive decline were inconsistent: processing speed (two of three studies positive), executive functioning (one of two studies positive) and global cognition (five of nine studies found a statistically significant association between hypertension and greater cognitive decline). The detailed results are discussed in the following paragraphs.

Two studies[275,276] found no significant association between either SBP or DBP and cognitive decline over 6 to 7 years. Cognitive outcomes were measured with the MMSE[275,276] and other memory tests.[275]

In a substudy of the ARIC cohort, Knopman et al. found a worsened performance on verbal fluency associated with hypertension but no association with delayed recall or processing speed.[260] Alves de Moraes and colleagues, in an earlier analysis of the full ARIC cohort[269] compared five different categories of hypertension with each of three cognitive tests and found that only subjects with uncontrolled hypertension (high SBP or high DBP on both followup

visits) and DSST subtest scores were significantly related. Peila and colleagues[163] found that never-treated hypertensives declined faster on a measure of general cognition, the Cognitive Abilities Screening Instrument (CASI; 1.46 points decline/year; range 0 to 100) than did hypertensives treated for 5 to 12 years (1.14 points of decline/year). However, differences between untreated hypertensives and those treated for 0 to 5 years and those treated > 12 years were not statistically significant, making importance of the finding unclear. Barnes and colleagues[271] gave subjects a shortened version of the MMSE several times over a study duration of 6 to 15 years (median 10 years). The study population was divided into tertiles defined by the slopes of the lines representing this change over time. Optimal cognitive functioning was defined by a slope of 0. Lack of hypertension was predictive of optimal cognitive functioning, with an OR of 1.22 (95 percent CI, 1.03 to 1.44). Tzourio et al.[278] found the strongest association between hypertension and cognitive decline, defined as a 4-point decline in MMSE scores over the 4-year followup of the study. When hypertension was defined as SBP ≥ 160 mmHg or DBP ≥ 95 mmHg, the OR for cognitive decline was 2.8 (95 percent CI 1.6 to 5.0). When hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, the OR decreased to 1.8 (1.2 to 2.9). The study population was younger than in other cohorts (mean age 65 years), and an MMSE decline of 4 points would represent a fairly severe decline. Waldstein and colleagues[279] reported a nonlinear relation of SBP with cognitive change as measured by tests of non-verbal memory and confrontational naming. Younger subjects with higher SBP made more baseline errors on the BVRT but improved over time, while older individuals with high SBP made more errors and got worse over time. Haan and colleagues[274] found that SBP that was a standard deviation above the mean was associated with a faster decline on the 3MS and the DSST. Glynn et al.[280] looked at the Boston EPESE cohort, a subset of which had blood pressure readings from 9 years prior to first brief cognitive tests followed by further cognitive tests 3 and 6 years later. No association was identified between various blood pressure levels and errors on a brief memory test or the short portable mental status questionnaire (SPMSQ) except for a single category of hypertension (SBP>160) and a greater increase in SPMSQ errors over time.

Other populations were less generalizable. Two studies[262,272] reported on the association in white male twin pairs from WWII. Hypertensives had a greater decline on the DSST, which was statistically significant using a one-sided p test,[262] but not on the MMSE or BVRT.[272] The same subjects with high blood pressure in mid-life showed greater decline in MMSE scores over 10 years when compared to those with low SBP (< 120 mmHg).

Kuo and colleagues[277] looked at subjects in the ACTIVE trial, which tested different cognitive training techniques. Subjects were followed over 2 years. Hypertensive subjects (defined by direct measurement but not use of antihypertensives) had faster decline in reasoning tests, while memory, speed of processing, and global cognition composite scores were not significantly affected. The authors found no meaningful (or statistically significant) interactions between the cognitive training intervention and the effect of hypertension on cognitive decline.

If there is a pattern to these isolated positive results, it is that they tended to be in tests associated with frontal lobe functioning (reasoning, working memory, etc). This is an area of the brain thought to be vulnerable to vascular insults, which could be expected to be more likely in hypertensive subjects.

One study was formed by the subjects in the SHEP trial (subjects were volunteers for blood pressure screening and had SBP 160 to 239 and DBP < 100, with randomization to antihypertensive or placebo).[273] The SHEP trials compared the effects of antihypertensive drugs versus placebo on cardiovascular outcomes; cognitive change was a tertiary outcome measured

by the Trails A and DSST. Duration of this substudy was only 1 year, and all subjects were hypertensive at trial initiation. Neither the antihypertension intervention nor the change in SBP was associated with changes in cognition over this brief period.

The Religious Orders cohort of retired clergy[108] had an older mean age of 75. The cohort was highly educated (mean of 18 years of education). Baseline blood pressures were low. No relationship was noted between blood pressure analyzed as a continuous variable and cognitive decline, defined by a global score from combining multiple tests, over 6 to 15 years. It is possible that individuals with hypertension selectively died prior to inclusion in this cohort, or that the limited variability of blood pressure levels prevented detection of any association.

In summary, while multiple cohorts have been examined for an association between hypertension and cognitive decline using various tests, the samples are as heterogeneous as are the outcomes, definitions of hypertension, and results. The strongest results were associated with subjects whose hypertension was untreated and whose cognitive decline was relatively severe. Some studies found results when multiple tests were compared individually with hypertension at baseline, raising the possibility that a positive result could arise by chance.

Table 48. Hypertension and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Solfrizzi et al., 2004[266] ILSA	Community cohort (1524)	3.5 years 113 incident MCI	Self-report or treatment or measured ≥ 90 or ≥ 140 in last two of three	Petersen's without requirement for subjective memory disorders and allowance for non-cognitive disability MMSE BSRT DCT	Age Educational level Total cholesterol HTN Coronary artery disease	RR for incident MCI: 1.20 (0.76 to 1.89)
Tervo et al., 2004[267] Kuopio community	Community cohort (548)	3.26 years (0.7) 65 incident MCI	≥ 160 or ≥ 95 or antihypertensive use	Petersen's criteria but no informant Visual Reproductive Test from the WMS Logical Memory Test (immediate and delayed) from the WMS-R Word List Recall (immediate and delayed) from CERAD Delayed Recall of the Constructional Praxis from CERAD NYU Paragraph Recall (immediate and delayed) Boston Naming Test (BNT) Trails A and B Block Design from WAIS-R MMSE	Age APOE Cardiovascular disease Cerebrovascular disease Sex Educational level DM Medicated HTN	OR for incident MCI 0.91 (95% CI 0.49 to 1.69)
Reitz et al., 2007[268] Northern Manhattan	Community cohort (918)	Mean 4.7 years 334 incident MCI	> 140/90 and self-report	Petersen's criteria but no informant 7 subtests of the Selective Reminding Test	Age Race Sex Educational level APOE e4	HR for incident MCI: 1.2 (95% CI 0.8 to 1.69)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
				Rosen Drawing Test Matching and recognition from Benton Visual Retention Test and identities and oddities subtests of the Mattis Dementia Rating Scale BNT COWA Wechsler similarities	Stroke DM Heart disease LDL level	
Alves de Moraes et al., 2002[269] (also published in Knopman et al., 2001[270]) 14-year data published by Knopman et al., 2009[260] ARIC	Community cohort (8058)	6 years	Self-report, use of antihypertensive meds, or SBP ≥ 140 or DBP ≥ 90 Four categories: Normal BP Incident HTN Partially controlled HTN (one or other visits had normal BP) Uncontrolled HTN	Delayed word recall test Digit symbol subtest Word fluency test	Age Race Sex Educational level DM	In comparing each (of 5) categories of HTN to normotensive subjects for each of the tests, the only significant difference was that between uncontrolled hypertensives and normotensives for the DSST scores. In data not shown this is limited to individuals over the median age of the cohort (> 56 years) at the first visit considered here.
Knopman et al., 2009[260] Same cohort as Alves de Moraes et	Community cohort (1130)	14 years	SBP > 140 DBP > 90 Use of antihypertensives in previous 2 weeks	Delayed word recall test DSST subtest WF	Age Race Sex Educational level Vascular factors Time Risk factor x time interaction	HTN as a dichotomous variable: non-significant association with DSST, DWR Difference of -0.113 per year on WF (p = 0.001; more decline in hypertensive subjects)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
al., 2002[269] and Knopman et al., 2001[270]) ARIC						
Barnes et al., 2007[271]	Cohort formed from SOF study (9704)	Median 10 years; range, 6 to 15 years	Self-reported history of HTN	MMSE over time, modified to a 26-point scale Subjects divided into maintainers, minor decline, and major decline defined by slopes of lines divided into tertiles	Age Educational level Baseline cognitive status Study site	Lack of HTN is predictive of maintaining optimal cognitive functioning with an adjusted OR of 1.22 (95% CI 1.03 to 1.44)
Carmelli et al., 1998[262] (Subjects from same cohort as Swan et al., 1998[272])	Community cohort (WWII twins) (410)	Cognitive change over approximately 10 years, BP measured over 25 years	Mean BP > 140/90 or use of antihypertensive medication	MMSE DSST BVRT	Age Race Sex Baseline cognitive scores Incident CVD	Hypertensives experienced a greater decline on the DSST but not MMSE or BVRT Relative risk (RR): MMSE: 1.16 DSST: 1.42 (one-sided $p < 0.05$) BVRT: 1.12
Swan et al., 1998[272] (Subjects from same cohort as Carmelli et al., 1998[262])	Community cohort (WWII twins) (317)	Cognitive change over approximately 10 years, BP measured over 25 years	Directly measured BPs averaged over first three waves, approx 15 years	MMSE DSST BVRT	Age History of stroke Educational level	Subjects with high mid-life SBP experienced a greater decline than those with low SBP (< 120) 10-year change in MMSE (SE): Low SBP: 0.04 (0.28) High SBP: -0.66 (0.36) DSST: Low SBP: -1.55 (0.69)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
						High SBP: -5.03 (0.84)
Gurland et al., 1988[273] SHEP	Cohort formed from an RCT (481)	1 year	BP directly measured	SHORT - CARE DSST Trails A	Age Race Sex Educational level, Baseline cognitive status Annual SBP Baseline SBP Baseline disability Drug status	Drug used in the RCT and change in SBP did not correlate with changes in cognition. According to text "there is a significant but weak association between the cognition outcome and baseline SBP" but no quantitative data are reported.
Haan et al., 1999[274] CHS	Community cohort (between 4700 and 5000 [unclear])	5 to 7 years (unclear)	Direct measure Calculations done for SBP > 158 (a SD over mean)	3MS DSST	Age Sex Race Incident stroke Education	Increase in BP of 1 SD over mean (21.84 mmHg) was associated with a decrease of 0.96 points in 3MS over 7 years and 0.53 points in DSST over 7 years (both $p < 0.0001$).
Hebert et al., 2004[275]	Community cohort (4284)	Baseline, 3 years, 6 years; 64% had all three visits, 36% had two	Self-report of antihypertensives at baseline and pill bottles maybe examined BP checked twice and averaged each visit	Four tests combined using z scores based on the population mean at baseline. Tests were: Immediate and delayed story recall MMSE Symbol Digit Modalities Test	Age Race Sex Educational level SBP or DBP (whichever was not examined)	Outcome was predicted annual change in global outcome score over a 6-year interval for 1 mmHg increase in BP. Neither SBP nor DBP were related to cognitive change. SBP: -0.0001 (-0.0003 to 0.00001) DBP: -0.00002 (-0.00036 to 0.00032 DBP entered as a quadratic term is said to be significant in a curvilinear fashion such that 75 mmHg has a minimum decline
Insel et al., 2005[276] Hispanic	Community cohort (1460)	7 years	Self reported hypertension or SBP ≥ 140	MMSE	Sex Age Education	Neither SBP nor DBP at baseline predicted cognitive decline.

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
EPESE					DM Income Heart disease Stroke HTN	This paper models the change in BP vs. the change in MMSE over time. The SBP line slope for the normotensives, which increases from visit 1 to 2, predicts cognitive decline.
Kuo et al., 2005[277] ACTIVE	Cohort formed from an RCT (2802)	2 years	BP directly measured Subjects divided into: Normal Pre-HTN HTN 1 (140-159/90-99) HTN 2(> 160/100)	MMSE, Hopkin Verbal Learning Test Related Word Lists Rey Auditory-Verbal Learning Test Unrelated Word Lists Rivermead Behavioral Memory Test Paragraph Recall task	Age Race Sex Educational level Baseline cognitive status Study site Intervention group Cardiovascular risk factors Tobacco use BMI	Subjects with stage 2 HTN had a faster decline in reasoning composite Subjects with stage 1 and 2 had faster decline in reasoning than normotensive subjects.
Peila et al., 2006[163] HAAS	Community cohort (1294)	Variable 4 to > 12 years	Direct measure or self-reported HTN or self-report of antihypertensive medication	CASI	Age Mid-life BMI Smoking CAD CVA Atherosclerosis APOE e4 Education	Annual decline in CASI score was greater for never treated hypertensives (-1.46) compared to treatment for 5 to 12 years (-1.14) and normotensives (-1.01), but was not statistically significant compared to 0 to 5 years treatment (-1.22) or > 12 years treatment (-1.08)
Shah et al., 2006[108] Religious Orders Study	Community cohort (retired clergy) (824)	Mean of 6.5 annual evaluations	Direct measurement and self-reports of HTN	Global score based on all tests: Word List Memory Word List Recall Word List Recognition Immediate and delayed recall of Story A from WMS-R East Boston Story (immediate and delayed) Verbal Fluency	Age Sex Education APOE e4 Use of antihypertensive medications	Investigators state that in a fully adjusted model "the null relationship persisted," but results are not shown. In evaluation using covariates for age, sex, education, SBP x time had estimate of 0.00 with SE 0.00 and p 0.237; DBP x time had estimate 0.000 with SE 0.001 and p = 0.232. Time itself had decrease of

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
				BNT Extended Range Vocabulary Test National Adult Reading Test Digits Forward and Backward from WMS-R Digit Ordering Alpha Span SDMT Number Comparison Judgment of Line Orientation Standard Progressive Matrices		0.036 points per year in global score.
Tzourio et al., 1999[278] EVA	Community cohort (1172)	~4 years	Direct measurement (SBP ≥ 160 or DBP ≥ 95) Those taking antihypertensives also considered to have HTN Chronicity defined as HTN at baseline and 2-year assessment	MMSE Cognitive decline defined as a 4-point drop over 4 years of study	Age Sex Education Income Depressive symptoms Alcohol APOE Baseline MMSE	OR for cognitive decline (with 95% CI): HTN: 2.8 (1.6 to 5.0) SBP > 140 or DBP > 90: 1.8 (1.1 to 2.9) Antihypertensives on both visits: 1.3 (0.3 to 4.9) Not taking at least once: 6.0 (2.4 to 15.0)
Waldstein et al., 2005[279] BLSA	Community cohort (847)	Visits every 2.32 (0.8) years, mean 2.7 (1.5) visits	Direct measurement once in each arm approximately 90 minutes post-breakfast, averaged	Digits Forward and Backward California Verbal Learning Test Benton Visual Retention Test Trails A and B Letter and Category	Age Education Alcohol use Smoking Use of antihypertensives Depression	"Nonlinear relation of SBP with longitudinal change on tests of non verbal memory and confrontational naming"

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
				Fluency BNT		
Yaffe et al., 2009[258] Health ABC	Community cohort (2509)	Visits years 1, 3, 5, and 8	Self-report or use of antihypertensive or SBP > 140 or DBP > 90	3MS change 'Maintainer'-slope of 0 or greater 'Minor decliner' slope > 0 but < 1 SD of mean of slopes 'Major decliner' slope > 1 SD	Age Race Education Reading level Work/volunteer status Caregiver Social support Living situation Self-rated health Alcohol Exercise Smoking Depression BMI DM History of stroke APOE status CRP IL-6 Triglycerides Fasting glucose	OR (95% CI) for maintainer vs. minor decliner; HTN 1.03 (0.83 to 1.28) For major decliner vs. minor decliner: 1.29 (0.97 to 1.73)
Glynn et al., 1999[280] Boston EPESE	Community cohort (3657)	BP 9 years pre-baseline then at 3 and 6 years	Direct measure	9-item SPMSQ 6-item East Boston Memory Test	Age Sex Educational level Time in study	BP at baseline or 9 years earlier was not associated with 6-year change in cognition. Only those with SBP ≥ 160 9 years prior to baseline had a greater increase in SPMSQ errors over time.

Abbreviations: 3MS = Modified Mini-Mental State Examination; APOE = apolipoprotein E gene; APOE e4 = e 4 allele of the apolipoprotein E gene; BMI = body mass index; BNT = Boston Naming Test; BP = blood pressure; BSRT = Babcock Story Recall Test; BVRT = Benton Visual Retention Test; CAD = coronary artery disease; CASI = Cognitive Abilities Screening Instrument; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; COWA = Controlled Oral Word Association test; CRP = C-reactive protein; CVA = cerebrovascular accident; CVD = cardiovascular disease; DBP = diastolic blood pressure; DM = diabetes mellitus; DSST = Digit Symbol

Substitution Test; DWR = delayed word recall; IL-6 = Interleukin-6; HR = hazard ratio; HTN = hypertension; LDL = low density lipoprotein; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NYU = New York University; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SBP = systolic blood pressure; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SE = standard error; SPMSQ = Short Portable Mental Status Questionnaire; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WF = Word Fluency Test; WMS = Wechsler Memory Scale; WMS-R = Wechsler Memory Scale-Revised

Hyperlipidemia. We identified one good quality systematic review that examined the relationship between total cholesterol and cognitive impairment and cognitive decline.[40] No formal quality assessment of included papers was done. Two studies examined the relationship between a mild cognitive impairment diagnosis and total cholesterol. One[266] examined cholesterol in late life and found a lower risk with higher cholesterol, but the confidence interval included 1 (RR 0.67; 95 percent CI 0.45 to 1.00). Another study[281] found total cholesterol in midlife of ≥ 6.5 mmol/L (251 mg/dL) to be related to incident MCI, with an OR of 1.9 (95 percent CI 1.2 to 3.0). It is possible that the method of screening for MCI in this latter study was insensitive to some cases, and this may have skewed the results.

Of the studies examining cognitive decline included in the systematic review, only two would have met our inclusion criteria. Kalmijn and colleagues[282] found no association between late-life cholesterol and cognitive decline (OR 1.38; 95 percent CI 0.75 to 2.55). Reitz et al.[283] also found no relationship (after Bonferroni correction) between cholesterol and cognitive decline.

Our own independent search identified two additional papers (Table 49; detailed evidence tables are provided in Appendix B). Knopman et al.[270] found no association between hyperlipidemia and declines on any test in a population initially aged 45 to 64 and followed a mean of 6 years. Word fluency, DSST, and DWR were the tests used. Packard et al.[284] identified no significant associations between LDL or HDL levels and performance in any tests in a cohort formed from subjects from a statin treatment trial and adjusted for treatment allocation who were followed a mean of 3.2 years with an initial age between 70 and 82 years. Tests given were MMSE, picture word recall test (involving immediate recall and recall after 20 minutes), Stroop Color and Word Test, and letter digit coding test.

As in the data concerning incident AD and total cholesterol levels suggest, lipid levels are not convincingly related to cognitive impairment by this available data. There was a trend toward a lower risk of cognitive decline with higher late-life cholesterol in one study,[266] but a lack of association in four others.[270,282-284]

Table 49. Total cholesterol and risk of cognitive decline

Study	Sample	Followup	Exposure	Case definition	Confounding adjustment	Results
Knopman et al., 2001[270] ARIC	Community cohort (10,610)	6.0 years (0.3)	Hypercholesterolemia, directly measured as LDL ≥ 140 or use of lipid lowering agent; fasting status not specified	Word fluency DSST DWR	Age Race Sex Educational level Site CNS-relevant medications	Hyperlipidemia not associated with declines on any test
Packard et al., 2007[284] PROSPER	Cohort formed from an RCT (5804)	Mean 3.2 years; range, 0.7 to 4.2	Directly measured twice at baseline	MMSE Picture-word learning test Stroop Color and Word Test Letter digit coding test	Age Sex Country Education History of vascular disease, MI, stroke, TIA, smoking, antihypertensive medication, BP, BMI, or DM Triglycerides Treatment allocation APOE e4 Baseline cognitive test scores	Differences between last on-treatment and the second of two baseline measures. Difference in changes scores reported (by LDL-C and HDL-C tertile). No significant difference for any cognitive measure Activities of daily living and independent activities of daily living: No significant difference by LDL-C or HDL-C tertile for either outcome

Abbreviations: APOE e4 = e 4 allele of the apolipoprotein E gene; ARIC = Atherosclerosis Risk in Communities; BP = blood pressure; BMI = body mass index; CNS = central nervous system; DM = diabetes mellitus; DSST = Digit Symbol Substitution Test; DWR = Delayed Word Recall; HDL = high density lipoprotein; HDL-C = high density lipoprotein cholesterol; LDL = low density lipoprotein; LDL-C = low density lipoprotein cholesterol; MCI = mild cognitive impairment; MI = myocardial infarction; MMSE = Mini-Mental State Examination; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; SD = standard deviation; TIA = transient ischemic attack; RCT = randomized controlled trial

Homocysteine. We identified four cohort studies[120,238,285,286] and a nested case-control study[237] involving 3409 subjects that examined the association between homocysteine and risk of cognitive decline (Table 50). Among the five studies, three were conducted in European communities,[237,285,286] and two in U.S. communities.[120,238] One study selected a sample of highly functioning elderly;[238] the other studies selected samples from general community populations. Three studies[237,238,286] used non-fasting homocysteine samples that may not measure bioavailable folate as well as fasting samples. Rather than specifying abnormal homocysteine levels a priori, all studies set thresholds based on population levels. Thresholds varied across studies. In the cohort studies, followup rates exceeded 80 percent. In the nested case-control study, 51 percent of survivors agreed to participate when approached at 10-year followup, and of these, only 68 percent provided blood for analysis. The duration of followup was relatively short in two studies (2 to 2.7 years),[285,286] and 4.7 to 10 years in the other studies. Three studies[237,285,286] used declines in the Mini-Mental State Examination (MMSE) to determine cognitive decline. Decline was evaluated as a continuous measure or using different thresholds for decline. The other two studies used multiple cognitive tests to compute a single summary score[238] or summary scores for several domains of cognitive function.[120] All studies adjusted results for multiple potential confounding variables.

Using a MMSE decline of greater than 1 point per year, Kalmijn et al.[286] found no significant association with tertiles of homocysteine. Dufouil et al.[285] evaluated the association using quartiles of homocysteine. The highest quartile (≥ 15 μmol/L) was associated with an increased risk for a ≥ 3-point decline in the MMSE over 2 years (OR 2.8; 95 percent CI 1.2 to 6.2). This 1- to 1.5-point average annual decrease in MMSE would represent a fairly rapid decline in cognition. Clarke et al.[237] evaluated the association between the 8-year change in homocysteine values and 10-year change in MMSE. Doubling of homocysteine was associated with more rapid decline on the MMSE, but when analyses were adjusted for other vitamin markers (B12, folate, methylmalonic acid), the association was no longer statistically significant.

Analyses of other cognitive outcomes showed inconsistent associations with baseline homocysteine values. Kado et al.[238] used a summary cognitive score and found no significant association with homocysteine, categorized by quartiles, and cognitive decline over 7 years in a population selected to be in the top third of cognitive and physical functioning (RR for highest versus lowest quartile 1.11; 95 percent CI 0.65 to 1.76). Luchsinger et al.[120] created summary scores for memory, language, and visuospatial domains. Comparing homocysteine values greater than the median (15.6 μmol/L) to values below the median, homocysteine was not associated not associated with a greater decline in any domain. Subjects were followed for a mean of 4.7 years. Dufouil et al.[285] found that homocysteine values greater than 15μmol/L were associated with greater decline on the DSST, finger tapping, and Trails B test.

The variability in subjects studied, classification of exposure, outcomes measured, and duration of followup may explain the variability in observed associations. However, given the small number of studies and the variability across multiple dimensions, no clear pattern can be determined.

In summary, we identified five studies that examined the relationship between baseline homocysteine and cognitive decline. Four of the five studies did not find an association between cognitive decline and homocysteine levels, and two studies found associations using differing definitions of exposure. There is no consistent association between homocysteine levels and cognitive decline.

Table 50. Homocysteine and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Kado et al., 2005[238]	Community (449)	7 years	Non-fasting plasma homocysteine	Summary cognitive score including naming, delayed recall, spatial memory recall, similarities	Age Sex Education Baseline physical function Smoking Second model added vitamins B6, B12, and folate	7-year cognitive decline, highest vs. lowest quartile of homocysteine: RR 1.44 (95% CI 0.91 to 2.09) Adjusted for B vitamins and folate, 7-year cognitive decline: RR 1.11 (0.65 to 1.76)
Dufouil et al., 2003[285]	Community (1107)	2 years	Fasting plasma homocysteine	MMSE decline of ≥ 3 points over 2 years Other tests also done	Age Sex Education Baseline cognition BMI Alcohol Smoking Hypertension Hypercholesterolemia Glycemic status Vascular disease Folate Vitamin B12	2-year cognitive decline, highest homocysteine quartile (> 1 5 µmol/L) vs. lowest (< 10 µmol/L): OR 2.8 (95% CI 1.2 to 6.2) Homocysteine ≥ 15 µmol/L associated with mean decrease of 0.26 points on MMSE for subsequent waves (p = 0.05) Other tests: Homocysteine > 15 µmol/L associated with greater decline on DSST and finger tapping tests
Kalmijn et al., 1999[286]	Community (702)	2.7 (0.5) years	Non-fasting plasma homocysteine	MMSE decline of > 1 point annually	Age Sex Educational level Baseline MMSE	1-year cognitive decline, highest vs. lowest tertile of homocysteine: OR 0.91 (95% CI 0.52 to 1.58); middle tertile (12.9 to 15.7 µmol/L): OR 1.14 (0.67 to 1.93)
Luchsinger et al., 2004[120]	Community (679)	4.7 years	Fasting plasma homocysteine	Standardized test scores averaged to evaluated three domains: memory language, and visuospatial	Age Sex Education APOE Stroke Creatinine Folate	Homocysteine > median (15.6 µmol /L) vs. less than median, beta coefficient = -0.04 (SE 0.03) greater decline on the memory score, p = 0.21 High homocysteine was not associated with greater decline in visuospatial or language scores

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
					Vitamin B12 Smoking status Diabetes mellitus Hypertension Cardiovascular disease BMI	
Clarke et al., 2007[237]	Community (472)	10	Non-fasting homocysteine (measured at year 2)	MMSE	Age Education Smoking Vascular disease Systolic BP APOE Methylmalonic acid Vitamin B12 Folate Holotranscobalamin	Doubling of homocysteine levels over 8 years (mean of 10 to 20 µmol/L), was not associated with greater annual decline in MMSE: beta coefficient (SE) = -0.033 (0.029) points/year

Abbreviations: APOE = apolipoprotein E gene; BMI = body mass index; BP = blood pressure; CI = confidence interval; DSST = Digit Symbol Substitution Test; MMSE = Mini-Mental State Examination; OR = odds ratio; RR = relative risk; SE = standard error

Other medical factors. Factors considered under this heading include sleep apnea, obesity, and traumatic brain injury (TBI).

Sleep apnea. We did not identify any good quality systematic reviews or primary studies that evaluated the association between sleep apnea and risk of cognitive decline.

Obesity. We did not identify any good quality systematic reviews that examined the relationship between weight and cognitive decline. We identified three prospective cohort studies that examined the effects of obesity on cognitive decline.[257,258,287] These studies are summarized in Table 51; detailed evidence tables are provided in Appendix B. Two of these were conducted in the United States,[258,287] while the other was conducted in Australia.[257] All three studies recruited participants from the community thereby decreasing bias in selection of the cohort; however, only two studies excluded participants with impaired cognition.[257,258] Most participants were over age 70 at the time of cognitive testing except in one study where the mean age was 62.5.[257] Two of the studies ascertained BMI by direct measurement of height and weight;[258,287] the remaining study calculated BMI from self-reported height and weight.[257] Cognitive decline was considered as a continuous variable in one study.[287] The other two studies categorized the variable as MCI[257] and as major and minor decliners, defined by the slope of cognitive decline being ≥ 1 SD below the mean and 0 < but no more than 1 SD below the mean, respectively.[258] The period of followup ranged from 4 to 8 years. Only one study compared the sample at baseline by exposure and found that persons with the highest BMI tended to be younger, female, and black,[287] while the others compared samples at baseline based on their outcome. There was no a priori calculation of the sample size in any of the studies, but all did control for potential confounders in the analysis.

Sturman et al.[287] included people with all levels of baseline cognitive function and showed that a higher BMI was associated with less cognitive decline over 6 years in both black (β = 0.0013, p = 0.009) and non-black subjects (β = 0.0021, p = 0.006). In a separate analysis limited to those who had MMSE scores greater than 24 (1010 participants), there was no relationship between obesity and cognitive decline over time in black (β = 0.0003, p = 0.415) or non-black subjects (β = 0.0008, p = 0.086). This latter analysis is of greatest relevance to our study question; however, it is important to bear in mind that this is a secondary analysis. Yaffe et al.[258] found that cognitive decline was associated with a higher BMI; however, this association was not statistically significant when investigators compared maintainers and minor decliners. They did find a statistically significant relationship between minor and major decliners where major decline was associated with higher BMI (OR 0.97; 95 percent CI 0.94 to 1.00). Cherbuin et al.[257] found that there was no statistically significant association between BMI and MCI (OR 1.01; 95 percent CI 0.93 to 1.10), but there was a significant association between BMI and any major cognitive decline (OR 1.05; 95 percent CI 1.05 to 1.09).

In conclusion, all three prospective cohort studies that have examined the association between weight and cognition are inconclusive. A possible explanation for this could be that the effect of weight on cognitive decline is small. It could also be the case that the extremes of weight have an adverse outcome which might be masked by considering weight to be single continuous variable. It is also notable that the studies did not measure lifetime or midlife BMI, as studies on BMI and AD show that the time of exposure to obesity is important. Also, change in weight, which has been shown to be a predictor for AD in some studies, was not considered. Future studies are needed to clarify the relationship between weight and cognitive decline and these studies need to consider age at exposure as well as change in weight.

Table 51. Obesity and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Sturman et al., 2008[287]	Community cohort (3885)	6.4 years	BMI	MMSE East Boston tests of Immediate Memory and Recall SDMT Combined Z score	Age Sex Education Time in study Stroke Diabetes Hypertension Heart disease	BMI did not have an association with cognitive function over time in black or white patients: Black: Coefficient 0.0003; P = 0.415 White: Coefficient 0.0008; P = 0.086
Yaffe et al., 2009[258]	Community cohort (2509)	8 years	BMI	3 MS Participants with predicted slopes of the 3MS scores of ≤ 0 were considered maintainers; 0 < but no more than 1 SD below the mean were considered minor decliners; ≥ 1 SD below the mean were considered major decliners	Age Race Educational level APOE genotype	Cognitive decline was associated with a higher BMI; however, this association was not statistically significant Maintainer vs. minor decliner: OR 0.99 (95% CI 0.96 to 1.02) Major vs. minor decliner: OR 0.97 (0.94 to 1.00)
Cherbuin et al., 2009[257]	Community cohort (2551; 2081 analytical sample)	4 years	BMI	DSM Published criteria for MCI AAMI, AACD , MNC, other cognitive decline and impairment on the CDR were grouped together as any MCD	Age Sex Educational level	Association of BMI with MCI: OR 1.01 (95% CI 0.93 to 1.10) Association of BMI with any MCD: OR 1.05 (95% CI 1.05 to 1.09)

Abbreviations: 3MS = Modified Mini-Mental State Examination; AACD = aging-associated cognitive decline; AAMI = age-associated memory impairment; APOE = apolipoprotein E gene; BMI = body mass index; CDR = Clinical Dementia Rating scale; CI = confidence interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; MCD = mild cognitive disorder; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MNC = mild neurocognitive disorder; OR = odds ratio; SD = standard deviation; SDMT = Symbol Digit Modalities Test

Traumatic brain injury (TBI). We did not identify any good quality systematic reviews or primary studies that evaluated the association between TBI and risk of cognitive decline.

Psychological and emotional health. Factors considered under this heading include depression, anxiety, and resiliency.

Depression. We identified 13 cohort studies, involving 32,969 subjects, evaluating the association between depression and categorical outcomes for cognitive impairment.[257,271,288-298] All studies excluded subjects with dementia, but most did not specifically exclude individuals with cognitive impairment that did not meet the threshold for dementia. An additional nine studies evaluated the association between depressive symptoms and changes on 26 different measures of cognition analyzed as a continuous measure. Because of the heterogeneity of continuous outcome measures and the similar results to studies using categorical outcomes, these studies will not be discussed in detail.[299-307]

Among the 13 cohort studies of interest, 6 studies each were conducted in Western Europe and the United States, all but one[291] in community samples. Almost all studies evaluated adults older than age 65. All studies assessed current depressive symptoms using a validated severity measure; two[257,296] also assessed antidepressant use at baseline. Seven studies reported incidence of MCI using similar definitions that required abnormal neuropsychiatric testing, change from prior cognitive status, absence of functional impairment, and not meeting criteria for dementia. The other six studies defined cognitive decline as a change in MMSE meeting or exceeding a specified threshold (1, 3, or 5 points) or in the lowest tertile. The average followup ranged from 1.5 to 6 years; the mean duration was at least 3 years for all but one study.[293] Most studies used methods to minimize selection bias and used generally appropriate analysis methods, including adjustments for confounding. However, only one study reported an a priori sample size calculation,[294] few controlled for psychotropic medication use, and followup rates were low or not reported in over half the studies.

Because of the variability in how studies categorized significant depressive symptoms, we did not compute a summary estimate of effect. Instead we summarized results qualitatively (Table 52). For the seven studies evaluating incident MCI, five showed an elevated risk for subjects with significant depressive symptoms. One study that found no association with depressive symptoms[296] found that antidepressant use increased risk. The study by Christensen et al.[289] had few incident cases of MCI and was likely underpowered. In contrast, the studies examining risk for decline on the MMSE were mixed. Three of the six studies showed an elevated risk for cognitive decline among those with depressive symptoms at baseline, one showed an elevated risk only for those with persistent depressive symptoms, and two showed no association. The variability in findings is not explained by differences in study population, exposure measurement, or study design. When all the studies using MCI and decline in MMSE are considered, the evidence suggests an association between depressive symptoms and cognitive decline.

Table 52. Depression and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Barnes et al., 2006[288]	Community cohort (2220)	6 years 296 cognitive decline	CES-D-10 = 3-7; CES-D ≥ 8 at baseline	MCI	Age Sex Education Race Baseline cognition Vascular disease	CES-D 3-7: OR 1.37 (95% CI 1.00 to 1.88) CES-D ≥ 8: OR 2.09 (1.46 to 2.97)
Cherbuin et al., 2009[257]	Community cohort (2082)	4 years 18 MCI 64 MCD	18-item Goldberg Depression & Anxiety Scale Antidepressant medication	MCI Any mild cognitive disorder (MCD)	Age Sex Education	For MCI, depressive symptoms (threshold not specified): OR 1.54 (95% CI 1.07 to 2.22) Antidepressant medication: OR 2.79 (0.38-20.57)
Christen-sen et al., 1997[289]	Community cohort	Mean 3.6 years 26 cognitive decline	18-item Goldberg Depression & Anxiety Scale	MCI	Age Education	No association, OR not reported
Geda et al., 2006[291]	Clinical cohort (840)	Mean 3.5 years 50 cognitive decline	GDS-15 ≥ 6 prior to MCI	MCI	Age Sex Education	HR 2.2 (95% CI 1.2 to 4.1)
Ravaglia et al., 2008[296]	Community cohort (864)	Mean 3.9 years 155 cognitive decline	GDS-30 ≥ 10 at baseline; antidepressant use	MCI	Age Sex Education APOE e4 Stroke risk score HTN Hyperhomo-cysteninemia	GDS: OR 1.1 (95% CI 0.5 to 2.0) Antidepressant use: OR 2.9 (1.3 to 6.6)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Wilson et al., 2007[297]	Community cohort (1256)	1 to 12 years 482 cognitive decline	CES-D-10 symptom count at baseline	MCI	Age Sex Education	RR 1.06 (95% CI 1.002 to 1.120) per symptom
Barnes et al., 2007[271]	Community cohort (9704)	Median 10 years 3202 cognitive decline	GDS-15 ≥ 6	MMSE decline in lowest tertile	Age Education Baseline cognition Study site	Elevated GDS associated with decline; OR not reported
Dufouil et al., 1996[290]	Community cohort (2726)	3 years 48 cognitive decline	CES-D ≥ 17 (men) & ≥ 23 (women) at baseline	MMSE decline ≥ 5 points	Age Sex Education Marital status IADL Baseline cognition	OR 0.8 (95% CI 0.3 to 2.1)
Geerlings et al., 2000[292]	Community cohort (2399)	Mean 3.1 years 251 cognitive decline	CES-D ≥ 16 at baseline	MMSE decline ≥ 3 points	Age Sex Education Memory complaints Baseline cognition	OR 1.07 (95% CI 0.70 to 1.62)
Ng et al., 2009[293] and Niti et al., 2009[308]	Community cohort (1487)	Mean 1.5 years	Chinese GDS ≥ 5 at baseline	MMSE decline ≥ 1 point	Age Sex Educational level Baseline MMSE APOE Vascular risk factors	OR 2.29 (95% CI 1.05 to 5.00) Men: OR 4.74 (1.25 to 17.8) Women: OR 1.29 (0.41 to 4.03)
Panza et al., 2008[294]	Community cohort (1524)	Mean 3.5 years 113 cognitive decline	GDS ≥ 10 at baseline	MCI	Age Sex Educational level Vascular risk factors	RR 1.25 (95% CI 0.85 to 1.84)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Paterniti et al., 2002[295]	Community cohort (1189)	4 years 161 cognitive decline	CES-D ≥ 17 (men) & ≥ 23 (women) at one time point (intermittent) or > 1 time point (persistent)	MMSE decline ≥ 3 points	Age Sex Education Alcohol use Tobacco use Psychotropic drugs Six chronic medical conditions Baseline cognition	OR 1.55 (95% CI 0.95 to 2.55) Episodic OR 1.22 (0.68 to 2.18) Persistent OR 2.1 (1.23 to 3.58)
Yaffe et al., 1999[298]	Community cohort (5781)	4 years 653 cognitive decline	GDS-15 ≥ 6; 3 to 5; vs. ≤ 2	MMSE decline ≥ 3 points	Age Education Baseline cognition Health status Exercise Alcohol use Functional status Clinic site	GDS ≥ 6: OR 2.1 (95% CI 14 to 3.1) GDS 3 to 5: OR 1.6 (1.2 to 2.1)

Abbreviations: APOE = apolipoprotein E gene; APOE-e4 = e 4 allele of the apolipoprotein E gene; CES-D = Center for Epidemiologic Studies Depression Scale (range 0-60; 10-item version scored 0-30); CI = confidence interval; GDS= Geriatric Depression Scale; HR = hazard ratio; HTN = hypertension; IADL = Instrumental Activities of Daily Living; MCD = mild cognitive disorder; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NR = not reported; OR = odds ratio; RR = relative risk

Anxiety. We identified four prospective cohort studies, involving 6297 mid- to late-life adults, examining the association between anxiety and cognitive decline.[257,309-311] All studies were conducted in community-based samples in Western Europe or Australia and followed subjects for up to 17 years.

The study by Wetherell et al.[311] followed 704 same-sex twins; the overall followup rate was 75.5 percent. Subjects with dementia at baseline or either of the two followup assessments were excluded from analyses. A baseline measure of neuroticism was used as a proxy for anxiety, and cognitive outcomes were assessed using 11 different measures. Analyses were adjusted for age, sex, and education level, but not for other psychiatric symptoms. There was no association between the 9-item neuroticism measure and change in cognition for any of the 11 different measures.

The study by Bierman et al.[309] followed 2351 adults aged 55 to 85. The followup rate at year nine was 62.5 percent, and dropout was associated with higher anxiety scores and lower cognitive performance, which may have biased the estimate of association. Anxiety was measured at multiple time points using the Hospital Anxiety and Depression Scale (HADS), and cognitive outcomes included a general measure of cognitive functioning (MMSE) and measures of fluid intelligence, processing speed, and episodic memory. Analyses were adjusted for age, sex, education, chronic disease count, depressive symptoms, alcohol consumption, and benzodiazepine use. There was no association between anxiety symptoms and cognitive decline for any of the cognitive measures.

The study by Gallacher et al.[310] followed 2358 non-demented men aged 48 to 67 for a mean of 17.3 years. Only those with baseline anxiety scores and followup (n = 1160, 48 percent) were included in the analyses. There were multiple baseline demographic and clinical differences between those with and without followup, potentially biasing the estimate of association. Anxiety was measured with the State Trait Anxiety Inventory (STAI) and dichotomized as high using the 31st percentile. Analyses were adjusted for age, education, marital status, cognitive function, and vascular risk factors. During followup, there were 174 cases of incident CIND and 69 cases of incident dementia. Elevated anxiety scores were associated with increased risk of CIND (OR 2.31; 95 percent CI 1.20 to4.44) and risk of the combined outcome of CIND or dementia (OR 2.19; 95 percent CI 1.24 to 3.88). A sensitivity analysis excluding those with cognitive impairment at baseline showed a stronger association.

Cherbuin and colleagues[257] followed 2082 cognitively normal adults for 4 years; followup exceeded 80 percent. Anxiety was measured using the Goldberg Anxiety/Depression Scale but a threshold for an abnormal result was not specified. Anxiety medication was assessed at baseline. During followup there were 18 incident cases of MCI and, using broader criteria, 64 cases of mild cognitive disorder (MCD). Anxiety symptoms and anxiety medications were not associated with MCI or MCD. A sample size or power calculation was not reported, but the study likely had low powered to exclude a clinically significant association.

In summary, four prospective cohort studies failed to find a consistent association between anxiety symptoms and cognitive decline. One study[309] was strengthened by a validated scale for anxiety, measured at multiple time points, but no study used a clinical or criterion-based diagnosis of anxiety disorders. Questionnaires, such as the HADS, correlate only moderately with clinical diagnosis; a criterion-based diagnosis may be a more clinically relevant measure of exposure.

Resiliency. We did not identify any good quality systematic reviews or primary studies that evaluated the association between psychological resiliency and risk of cognitive decline.

Medications. Prescription and non-prescription drugs considered under this heading include statins, antihypertensives, anti-inflammatories, gonadal steroids, cholinesterase inhibitors, and memantine.

Statins. Our search identified four cohort studies examining the relationship between statin use and cognitive decline.[153,312-314] A total of 6827 older adults (mean age > 70 years in all studies) were involved. All studies were conducted in the United States; three drew samples from the community. Followup ranged from 1 to 12 years. Three of the four studies reported measures of global cognition, while the fourth[312] reported executive function. Three studies screened for and excluded subjects with dementia. The fourth study[312] recruited a consecutive sample of veterans from primary care settings, with a mean age of 75 years old, but did not screen for dementia. Only one study selected subjects in a manner that minimized selection bias and baseline inequalities between exposed and unexposed groups.[313] Two of the four studies classified statin use only at baseline.[312,314] Data were analyzed appropriately and controlled for confounders.

Due to incomplete reporting and heterogeneity in study designs, a summary estimate of effect was not calculated. As summarized in Table 53, results were mixed. The study by Bernick et al.[313] was the largest, assessed statin use annually, used multiple control groups, and evaluated annual change for a mean of 5.1 years using a well-validated global measure of cognitive change. In an analysis adjusted for age, sex, education, race, APOE e4, and baseline cholesterol, the difference in mean rate of change in the Modified Mini-Mental State Examination (3MS) between continuous statin users compared to subjects for whom treatment was recommended but not taken did not differ significantly (0.40 annually; 95 percent CI -0.03 to 0.87). For continuous statin users compared with subjects in whom lipid lowering treatment was not recommended, the difference in mean rate of 3MS change favored statin use (0.49; 95 percent CI 0.04 to 0.95). In summary, a limited number of observational studies, some with important methodological limitations, do now show a consistent association between statin use and cognitive decline in older adults.

Table 53. Statins and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Agostini et al., 2007[312]	Clinical cohort (756)	1 year	Any use at baseline ; medication bottles, medical record	Trails B	Age Race Education Alcohol use Tobacco use Charlson comorbidity Dementia Medication count Primary care visits IADL Cholesterol History of MI or PVD Liver disease Baseline Trails B	No significant difference
Arvanitakis et al., 2008[153]	Community cohort (929)	1 to 12 years	Any statin during study; pharmacy records	Battery of test summarized into: global cognition, memory, perceptual speed, visuospatial ability	Age Sex Education	No significant difference for global, memory, perceptual speed, or visuospatial measures
Bernick et al., 2005[313]	Community cohort (3334)	5.1 years	None, intermittent, continuous; medication bottles	3MS	Age Sex Race APOE e4 Cholesterol	Mixed results: less decline with statin use compared to those not requiring lipid treatment, but no significant difference compared to those in whom lipid lowering treatment recommended but not taken
Szwast et al., 2007[314]	Community cohort (1808)	3 years	Any statin use; medication bottles at baseline	CSI-D	Age Sex Education APOE e4	Less decline in statin users

Abbreviations: 3MS = Modified Mini-Mental State Examination; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; CSI-D = Community Screening Interview for Dementia; IADL = Instrumental Activities of Daily Living; MI = myocardial infarction; PVD = peripheral vascular disease; Trails B = Trail Making Test Part B

In summary, data from observational studies were limited and did not show a consistent association between statin use and cognitive change. Two large RCTs, discussed under Question 4, also did do not show an association between statin use and cognitive change.

Antihypertensives. Two studies were identified examining the impact of antihypertensives on cognitive decline (Table 54).[267,278] Tervo et al.[267] looked at risk factors for incident MCI diagnosed using very modified Petersen's criteria in a sample from Kuopio, Finland. Self-report of antihypertensive use was elicited during a structured interview. It is not clear that the indication for the antihypertensive was elicited, but 44 percent of the overall sample had directly measured HTN (≥ 160/95). Diagnosis of MCI was based primarily on a test of delayed recall. Over a 3.26 year followup, there was no statistically significant impact of antihypertensive use on incident MCI; adjusted OR 1.61 (95 percent CI 0.87 to 2.99).

In the Tzouri study[278] of the Epidemiology of Vascular Aging (EVA) cohort from Nantes, France, cognitive decline was defined as a 4-point decrease in the Mini-Mental State Examination (MMSE) over 4 years. A 4-point decline in the MMSE would represent a significant decline in cognitive function, and was found in 8.5 percent of the sample. Again, the use of antihypertensives was not found to be protective against cognitive decline in the overall sample (as compared to those with normal measured BP and not on antihypertensives; adjusted OR 1.1; 95 percent CI 0.7 to 1.7). However, among subjects with HTN, the risk of cognitive decline was decreased in those taking antihypertensive medication at baseline and followup compared to those not taking antihypertensives at either time.

Both studies evaluated relatively young populations. The mean age in Tervo[267] was 67.7 years and in Tzourio[278] 65 years. Both studies were of relatively brief duration. Cognitive decline would be expected to be fairly uncommon under these circumstances and definitions of decline.

In summary, the limited evidence from observational studies does not support an association between antihypertensive use and lower risk for cognitive decline.

Table 54. Antihypertensives and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Tervo et al., 2004[267] Inhabitants of Kuopio community (Finland)	Community cohort (806)	3.26 years Cases of MCI: 65	Self-report of antihypertensives	Modification of Petersen criteria (no requirement for subjective complaint, no ADL requirement, and no informant): Scoring 1.5 SDs below average in delayed recall in logical memory or visual reproduction memory, with a CDR score of 0.5 and no dementia were called MCI	Age Sex Education APOE e4 Cardiovascular disease Cerebrovascular disease DM HTN	OR (95% CI) for conversion to MCI for medicated HTN in the fully adjusted model: 1.61 (0.87 to 2.99)
Tzourio, et al., 1999[278] Nantes, France	Community cohort (1052)	4 years Cases of cognitive decline at 4 years: 98	Self-report and medication bottle review	Decline of 4 points, or more, on MMSE (over 4 yrs)	Age Sex Education Income Depressive symptoms APOE e4 Baseline MMSE	Overall OR (95% CI) for cognitive decline with antihypertensives 1.1 (0.7 to 1.7); as compared to those with normal BP and no antihypertensive use For hypertensive subjects taking antihypertensives at baseline and 2 years: OR (95% CI) for cognitive decline 1.3 (0.3 to 4.9) If not taking antihypertensives at either time OR (95% CI) for cognitive decline 6.0 (2.4 to 15.0)

Abbreviations: ADL = activities of daily living; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; BP = blood pressure; CDR = Clinical Dementia Rating scale; CI = confidence interval; DM = diabetes mellitus; HTN = hypertension; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; OR = odds ratio; SD = standard deviation

Anti-inflammatories. Our search identified six cohort studies examining NSAID use and risk of cognitive decline.[240,270,315-318] These studies are summarized in Table 55; detailed evidence tables are provided in Appendix B. The classification of NSAID exposure was variable ranging from any use, to use before a certain age, to use for a variable duration of time. All of the studies evaluated decline over time in cognitive testing. All used memory tests. Other tests, as listed in Table 55, were added to individual studies. Studies by Hee Kang et al.[318] and Grodstein et al.[317] used a global test score formed from the combination of the tests given. Cognitive decline in the Cache County cohort[240,315] was defined by change in the 3MS, a measure of general cogniton measure using memory, orientation, and similarities among other items.

Five studies used community cohorts from the United States and one used a cohort from Amsterdam.[316] Two of the studies examined the same Cache County cohort, one evaluating NSAIDs alone,[315] the other evaluating the combination of NSAIDs with vitamins C and E.[240] In total, approximately 32,600 subjects were included from the five unique cohorts. Followup ranged from 2 to 9 years. Three studies restricted analysis to subjects without cognitive impairment at baseline.[240,315,318] Three studies did not eliminate cognitively impaired subjects when forming the cohorts, but one[316] had a mean baseline MMSE of 27.5, suggesting few subjects had significant cognitive impairment, and another[270] formed the cohort in middle age (47 to 70 years old) when prevalent impairment would be expected to be low. The CHAP cohort[317]did not limit inclusion to cognitively intact subjects and enrolled subjects with a mean baseline age of 79.9, suggesting that there may be a significant level of cognitive impairment in the sample. Cognitive impairment among participants could differentially bias the recollection of exposure.

Fohuti et al.[240] found that subjects using vitamin C, vitamin E, and NSAIDs who had at least one APOE e4 maintained cognitive functioning as opposed to declines in every other group. Hayden and colleagues,[315] examining the same Cache County cohort, found a protective effect of NSAIDs that was most beneficial when NSAIDs were started before age 65 and when at least one e4 allele was present. Mean age at baseline for the Cache County study was approximately 74 years. Recall of NSAID use decades earlier are of unclear accuracy. Grodstein[317] found slower rates of decline with longer NSAID use (5+ years) as compared to no use. Information on duration of NSAID use was collected 3 years after baseline (length of followup 3 to 9 years). It is possible that information on duration of use is more likely to be biased than the data on any NSAID use collected at baseline in those subjects developing cognitive deficits. However, a sensitivity analysis eliminating subjects with baseline cognitive scores in the bottom 10 percent was performed and did not show substantially different results. Grodstein et al.[317] found more protective effect in this relatively more intact group, especially those on NSAIDs longer. Jonker and colleagues found lowered odds ratio for decline on tests of delayed recall but confidence intervals were wide and included no effect.[316] An analysis of the large Nurses Health Cohort did not show an association between global cognitive decline and aspirin use or NSAID use of at least 8 years (RR for substantial decline 0.77; 95 percent CI 0.57 to 1.05).[318] Finally, another large cohort study found no association between NSAID use and cognitive decline on any of three measures.[270]

In summary, results from five cohort studies are inconsistent regarding the association between NSAIDs and cognitive decline. Several studies find no association between NSAID use and cognitive decline and no studies find an association of sufficient magnitude that the impact of unaccounted confounders can be dismissed. The Cache County cohort found protective effects in some subgroups only. Results from the CHAP cohort may be biased given the unknown

cognitive status of the cohort at baseline and the collection of duration of use data a few years into the study. There is limited support, based on a subgroup analysis, for a greater effect of NSAIDs when used at younger ages, for a longer duration, along with vitamin supplements and in those with at least one e4 allele.

Table 55. NSAIDs and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Fotuhi et al., 2008[240] Cache	Community cohort (3376)	Up to 8 years (0, 3, 8 years)	Self-report, pill bottles, probe questions At baseline asked about preceding 2 weeks	3MS	Age Sex Educational level DM Cerebrovascular accident APOE status	Study looked at Vitamins E&C and NSAIDs. Only among those using all three were there significant findings: Among e4 carriers, there was maintenance (0.65 points; 95% CI -0.58 to 1.89). Non users with e4 lost 3.77 points (-4.53 to -3.01) over the 8 years of the study For NSAIDs alone, e4 carriers changed by -3 points (95% CI -4.17 to -1.83), non e4 carriers with NSAIDs alone declined by -3.13 points (-3.83 to -2.43).over the 8 years of the study.
Hayden et al., 2007[315] Cache (same cohort as above)	Community cohort (3383 at start; 3294 after 3 years; 2235 after 8 years)	3 and 8 years	Self-report, pill bottles, probe questions At baseline asked about preceding 2 weeks	3MS	Age Sex Education APOE DM Cerebrovascular accident Followup time Quadratic term for time	Difference per year: <u>NSAID use before age 65:</u> No APOE e4: 0.10 points/year (95% CI -0.05 to 0.25; p = 0.19), so no change over time compared to non-users With an APOE e4: 0.40 points/year (95% CI 0.18 to 0.63; p = 0.0005), suggesting an association with maintained scores in this subset <u>NSAID use after age 65:</u> No APOE e4: -0.16 points/year (95% CI -0.30 to -0.03; p = 0.002), (suggesting greater decline in non-e4 carriers starting NSAIDs late as compared to non-NSAID users With an APOE e4: 0.06 points/year (95% CI -0.15 to 0.27; p = 0.56), suggesting no association with maintained scores
Jonker et al., 2003[316] LASA	Community cohort – groups of interest selected retro-	3 years	Prescription meds queried and prescription pill bottles examined at baseline and	MMSE AVLT Coding task	Age Sex Educational level Baseline MMSE score	ORs for cognitive decline provided for any NSAID (including aspirin), NSAIDs excluding aspirin, and aspirin alone for each of three tests (immediate recall, delayed recall and coding). Choosing delayed recall (OR [95%

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
	spectively (612 chosen from community sample) 475 who did not use NSAIDs 137 who did use prescription NSAIDs at both visits		followup visit		Vascular disease DM Rheumatoid arthritis	CI]): NSAIDs (including aspirin): 0.59 (0.27 to 1.27) NSAIDs (excluding aspirin): 0.68 (0.19 to 2.39) Aspirin only: 0.55 (0.22 to 1.40) There was a protective effect for aspirin only (low-dose predominantly) and only in subjects > 75 years of age
Grodstein et al., 2008[317] CHAP (Chicago)	Community cohort (4409)	Up to 9 years	Pill bottles, self - report Baseline and cycle 2 (after 3 years)	East Boston Tests of Immediate Memory and Delayed recall MMSE SDMT	Age Race Sex Educational level Interaction of time with each	In the analysis of the cohort with the bottom 10% removed, the aspirin data are not shown, but are stated to be "largely unchanged" over the analysis of the whole sample, which found no difference in the yearly rate of cognitive decline. Comparing participants (excluding bottom 10%) with short history of NSAID use (< 5 years) to no NSAIDs, difference of annual decline of 0.009 SD units (p = 0.02), with longer duration of use (5+ years) difference 0.013 (p = 0.012); data not otherwise shown Standard units per their global scale
Hee Kang et al., 2003[318] Nurses Health cohort	Community cohort (13,255)	2 years	Self-report (by nurses) in 1980 and every 2 years until 1998 NSAIDs as never, past, current, infrequent, and	TICS Delayed recall of a 10 word list East Boston memory test (immediate and delayed)	Age Baseline scores Perceived change in memory Cigarettes Education	Using global score, longer term aspirin users had no difference in decline: RR 0.91(95% CI 0.70 to 1.19) For other NSAIDs, longer term users (8+years) had lower risk of "substantial decline": RR 0.77 (95% CI 0.57 to 1.05)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
			current regular by numbers of years	Verbal fluency Digit span backwards Calculation of a global score Substantial decline defined as decline of ≥ 3 on TICS and worst 10% of distribution of decline for the global score	Alcohol BMI Physical activity HRT DM HTN Hypercholesterolemia Depression Cardiovascular disease	RR also given for individual tests
Knopman, 2001[270]	Community cohort (10,963)	6 years	Self-report, pill bottles Subjects asked at 3 years (visit 2) about previous 2 weeks	DWR DSST WF	Age Race Sex Educational level Site CNS-relevant meds (antipsychotics, antidepressants, anxiolytics, opiates, anticonvulsants, antineoplastic agents)	Adjusted mean change in individual tests per risk factor reported "NSAID use (and several others) not associated with declines on any of the cognitive tests"

Abbreviations: 3MS = Modified Mini-Mental State Examination; APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; AVLT = Auditory Verbal Learning Test; BMI = body mass index; CI = confidence interval; CNS = central nervous system; DM = diabetes mellitus; DSST = Digit Symbol Substitution Test; DWR = delayed word recall; HRT = hormone replacement therapy; HTN = hypertension; MMSE = Mini-Mental State Examination; NSAID(s) = non-steroidal anti-inflammatory drug(s); OR = odds ratio; RR = relative risk; SD = standard deviation; SDMT = Symbol Digit Modalities Test; TICS = Telephone Interview for Cognitive Status; WF = Word Fluency Test

Gonadal steroids. We identified a single good quality systematic review that examined the association between hormone replacement therapy and cognitive decline.[38] The review identified nine RCTs and eight cohort studies. Ten studies were from the United States, four from European countries, and three from Canada. The nine RCTs are discussed separately under Question 4, below. Of the eight cohort studies, six were rated as having fair quality and two as poor. The cohort studies included 15,298 subjects ranging in age from 59 to 77 years, with duration of followup ranging from 1.5 to 15 years. The formulation of estrogen varied in composition, dose, and method of administration. Most subjects received an estrogen formulation that did not include a progestin.

Studies were not combined because more than 40 different tests were used to assess cognitive function. Thirty of these tests were used in a single study, and seven tests were used in more than two studies, but test administration was not always uniform. Verbal memory using the immediate verbal recall test was examined in four studies and showed a benefit of estrogen treatment in one study. Delayed verbal recall was improved by estrogen treatment in two of three studies, while visual memory improved in one of two studies. Attention tasks were divided into complex attention (0 of 3 positive studies) and mental tracking (0 of 3 positive studies). Most of the studies reporting benefit noted an effect of estrogen on attention tasks and involved women with menopausal symptoms. Abstract reasoning was shown to be improved by estrogen treatment in one of two studies, and mental status, as measured by an improved score in a dementia screening examination, was improved in two of five studies. Verbal fluency was reported to be improved in one of four studies, with users of estrogen more fluent in naming than non-users. The review authors concluded that estrogen does not consistently enhance asymptomatic women's cognitive performance on formal testing.

Our search identified one new observational study published since 2001 (Table 56; a detailed evidence table is provided in Appendix B). Ryan et al. examined the association of self-reported, life-time estrogen exposure to late-life cognition in a prospective cohort study involving 996 French women aged 65 or older.[319] A battery of tests – including the MMSE, the 5-word Test of Dubois; Isaacs Set Test; semantic fluency; BVRT; MMSE; and Trails A and B – was performed at baseline, 2, and 4 years. In the fully adjusted model which accounted for age, education, and baseline test performance, the authors found no association of estrogen use with cognitive change.

In summary, there may be a slight benefit for symptomatic postmenopausal women in tests of verbal memory, vigilance, reasoning, and motor speed, which could be mediated by symptom relief. Available data does not support a consistent benefit of estrogen use in modifying cognitive decline. There is insufficient evidence to determine the optimal formulation of estrogen; the dose, duration, and onset of treatment; or if progestins attenuate the effect of estrogen.

Table 56. Gonadal steroids and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Ryan et al., 2009[319] ESPRIT study	Community cohort (996)	4 years (testing at 2 and 4 years)	Lifetime estrogen exposure Self-report of reproductive factors associated with estrogen exposure and use of exogenous hormone treatment	Substantial decline on cognitive tests defined as lowest quintile of the difference between baseline score and score at either of the followup visits Tests used: 5-word Test of Dubois; Isaacs Set Test; semantic fluency; BVRT; MMSE; Trails A and B	Age Educational level Marital status Depressive symptoms Caffeine intake Physical impairment Medical conditions Baseline cognitive status	In fully adjusted model, no association between lifetime estrogen exposure and risk of substantial decline on any cognitive measures

Abbreviations: BVRT = Benton Visual Retention Test; MMSE = Mini-Mental State Examination; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B

Cholinesterase inhibitors. We did not identify any systematic reviews or primary studies that evaluated the association between cholinesterase inhibitors and risk of cognitive decline.

Memantine. We did not identify any systematic reviews or primary studies that evaluated the association between memantine and risk of cognitive decline.

Social, Economic, and Behavioral Factors

Early childhood factors. We identified three eligible cohort studies that examined the association between childhood factors and cognitive decline in later life.[173,320,321] These studies are summarized in Table 57; detailed evidence tables are in Appendix B. One of the studies reported a categorical outcome;[321] the other two reported continuous outcomes of cognitive decline.[173,320] Given the small number of eligible studies, the studies reporting continuous outcomes are included in the current discussion. All three of the studies used community samples in the United States, and one of the studies included individuals residing in religious order facilities.[173] The length of followup ranged from 2 to 5.6 years. The cognitive status of participants differed across the studies. One study[320] included all participants who completed cognitive testing at a minimum of two time points, so some individuals may have had dementia at baseline. The other two studies[173,321] included only individuals who were non-demented at baseline. All of the studies at least partially used sample selection methods to minimize selection bias. All of the studies collected exposure data using self-report of a range of childhood factors; one study also used public records.[173] There was no objective validation of the indices derived to represent childhood socioeconomic status or childhood cognitive milieu.

The studies did not compare baseline characteristics between those exposed and unexposed, but one compared baseline differences by outcome groups (i.e., those who had cognitive decline versus those who did not).[321] The case definitions and cognitive outcomes for the studies are described in Table 57. The analyses appear generally appropriate and controlled for relevant potential confounders, but none of the studies conducted a priori sample size calculations. Two studies found no association between early life socioeconomic status or childhood cognitive milieu and cognitive decline in later life.[173,320] The third study used a Japanese-American cohort and found that numerous factors associated with stronger affiliation with Japan or the Japanese culture were associated with protection against cognitive decline in later life.[321] For select variables that allowed graded responses, the study found a dose-response effect where the greater the exposure to Japanese culture the less likelihood of cognitive decline. The differences in the sample characteristics and the childhood factors examined among these three studies make drawing conclusions difficult. The authors of the Japanese-American cohort study point to a number of differences between the Japanese and American cultures that may explain their findings. Based on the two studies using predominantly individuals born and raised in the United States, there does not appear to be a strong influence of childhood socioeconomic status or childhood cognitive milieu on cognitive decline in later life.

Table 57. Childhood factors and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Everson-Rose et al., 2003[320]	Community cohort (4398)	5.3 years (mean)	Childhood socioeconomic position index derived from self-report of: (1) parental educational attainment, (2) parental occupational prestige, (3) family financial status as a child Childhood cognitive milieu index derived from self report of: (1) frequency of someone in household having been read to, (2) told stories to, or (3) played games with as a child.	Global composite index of scores on the MMSE, the immediate and delayed recall of the East Boston Story, and the oral version of the Symbol Digit Modalities Test	Age Race Sex Educational level	Rate of cognitive decline for 1-unit increase in childhood socioeconomic position index: β = -0.003 (95% CI -0.009 to 0.003; p = 0.32) Rate of cognitive decline for 1-unit increase in childhood cognitive milieu index: β = -0.0008 (95% CI -0.004 to 0.002; p = 0.62) was associated with less cognitive decline
Wilson et al., 2005[173]	Community cohort (some lived in religious order facilities) (859)	5.6 years	Self-report and county public records Information collected by self-report: (1) parental education, (2) paternal occupation, (3) number of children in the family, and (4) participant's education level. Information collected from public records for the participant's county of birth: (1) literacy rate, (2) percent of children in county attending school, and (3) the Duncan socioeconomic index for head of households for the county.	Global composite index of scores on the MMSE, the immediate and delayed recall of the East Boston Story, and the oral version of the Symbol Digit Modalities Test	Age Sex Education	Rate of cognitive decline for 1-unit increase in childhood household socioeconomic status: β (SE) = -0.01 (0.01); p = 0.32 Rate of cognitive decline for 1-unit increase in childhood county socioeconomic status: β(se) = 0.01 (0.01); p = 0.10 Results were generally similar for the individual cognitive domains
Graves et al., 1999[321]	Community cohort	2 years	Self-report of the following information: (1) migration history, (2)	Dichotomous outcome of "decliners" vs.	Age Sex	Factors associated less with decliners: Japanese is only/mostly the home language: OR

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
	(1604)	144 decliners 1455 non-decliners	education, (3) number of years lived in Japan before age 18 yr, (4) age at which English became main language spoken at home, (5) language usually spoken at home currently, (6) current facility with reading and writing Japanese, (7) friends growing up being mainly Japanese vs. non-Japanese, or even number of both, (8) current friends Japanese, non-Japanese or even number of both, (9) current religion, (10) diet consistent of mainly Asian food, Asian and western food equally or mainly western food.	"non-decliners." Decliners defined as individuals who declined 5.15 points (equal to -1.0 SD) on the Cognitive Abilities Screening Instrument (CASI).	Educational level Baseline cognitive status Followup time	0.45 (95% CI 0.23 to 0.86; p < 0.01) English was the home language after age 40 yr: OR 0.42 (0.21 to 0.81; p < 0.01) Baseline interview in Japanese: OR 0.38 (0.21 to 0.69; p < 0.01) Generation Issei (born in Japan): OR 0.28 (0.13 to 0.58; p < 0.01) or Kibei (born in U.S., Japanese education): OR 0.58 (0.33 to 1.0, p < 0.05) compared to U.S. born and educated Any education in Japan: OR 0.44 (0.27 to 0.73; p < 0.01) Lived in Japan from 1 to 7 years: OR 0.46 (0.23 to 0.91; p < 0.05) or lived in Japan from 8 to 15 years: OR 0.38 (0.19 to 0.78; p < 0.01) or lived in Japan from 16 to 18 years: OR 0.32 (0.15 to 0.69, p < 0.01) compared to 0 years Reads/write Japanese with no difficulty: OR 0.42 (0.23 to 0.77; p < 0.01) or reads/writes with difficulty: OR 0.96 (0.62 to 1.47) compared to does not read/write Japanese Current friends mostly Japanese: OR 0.64 (0.44 to 0.93; p < 0.01) Past friends mostly Japanese: OR 0.91 (0.63 to 1.33) Eastern religion (Buddhist, Shinto): OR 1.34 (0.87 to 2.07) Eat only Asian foods: OR: 0.96 (0.62 to 1.49)

Abbreviations: CASI = Cognitive Abilities Screening Instrument; CI = confidence interval; MMSE = Mini-Mental State Examination; OR = odds ratio; SD = standard deviation; SE = standard error

Education/occupation. As described above (under Key Question 1), we consider educational and occupational factors as subcategories under a single heading.

Education. We identified eight eligible cohort studies that had a categorical outcome.[183,258,267,322-326] We also review an additional six studies that had a continuous outcome because they provide information on population subgroups of interest, such as different ethnic groups[327-329] or different APOE genotypes.[330-332] In the majority of these studies, the focus was on investigating the risk of cognitive decline and years of education completed, but in a few studies, education was only one of several risk factors examined in relation to cognitive decline. The studies are summarized in Table 58; detailed evidence tables are provided in Appendix B. Seven of the studies used community samples in the United States,[258,323-325,327-329] one used a health maintenance organization sample in the United States,[330] three used community samples in Europe,[322,326,332] one used a sample in Europe that included participants from both the community and institutions,[267] one used a community sample in Australia,[331] and one used a religious order sample in the United States.[183] At baseline, participants were non-demented in some studies[322-324,330,332] and cognitively normal in some others.[183,267,327] In other studies, those with mild cognitive impairment and dementia were not specifically excluded;[325,326,328,329,331] however, given the length of the followup period[328,329] or the baseline age of the sample,[331] it is likely that the majority of the participants were non-demented at baseline in most of these studies. The final study[258] included only individuals with a baseline 3MS score > 80 in an attempt to exclude those with dementia. Length of followup ranged from 1 to 11 years. Exposure was determined based on self-reported information about years of education completed; this is a standard and well-accepted method of data collection for this information. One study examined the association between literacy level as measured by a standard neuropsychological test and cognitive decline.[327] Most of the studies used sample selection methods to minimize selection bias; however, one study required that participants agree to brain donation at the time of death, and this may have introduced some selectivity into the sample.[183] One other study only partially used sample selection methods to minimize selection bias.[322] Definitions of cognitive decline varied among the studies and are described in Table 58. In all but one study[331] analyses were appropriate and controlled for relevant potential confounders.

Among the eight studies that had categorical outcomes, four reported that having fewer years of education was associated with an increased risk of cognitive decline on at least some of the cognitive measures used,[258,323-325] and the odds ratio for the fifth study[326] was in the same direction but did not reach statistical significance. An additional two studies reported that having fewer years of education was associated with an increased risk of incident MCI.[183,267] In general, the association was strongest at the extremes of high and low education, thus suggesting a dose-response pattern even when the association was not significant at all intermediary education levels. In the one study that did not find a significant association between education level and cognitive decline, the education level for the sample was quite low.[322]

In contrast to the studies that used categorical outcomes, the studies that used non-categorical outcomes typically did not find an association between years of education and cognitive decline. Four studies reported no association between years of education and rate of cognitive decline in their total samples.[329-332] A fifth study[328] found only a non-linear association such that the rate of cognitive decline at average or high levels of education was slightly increased during earlier years of followup, but slightly decreased in later years in comparison to low levels of education. The sixth study[327] reported that after controlling for education, participants with lower literacy were more likely to have faster decline in cognition.

These six studies using continuous variables also examined the association between years of education and longitudinal cognitive performance in selected subgroups of the samples. The three studies that reported results comparing ethnic subgroups showed few differences across the subgroups. The study by Wilson and colleagues[328] showed no differences between whites and African-Americans for the association between level of education and cognitive decline. Manly and colleagues[327] reported no significant differences between whites, Hispanic and African-Americans regarding the association between literacy level and rate of cognitive decline. The study by Karlamangla and colleagues[329] reported only one difference among multiple ethnic groups. They found that among non-Mexican Hispanic Americans, a greater number of years of education was associated with less cognitive decline over time.

Four studies (three using continuous outcomes and one using a categorical outcome) assessed potential interactions between APOE genotype and education, and each study reported different results. Winnock and colleagues[332] found no interaction between APOE genotype and education in their association with cognitive decline. Kalmijn and colleagues[326] reported that APOE e4 non-carriers with less education tended to show greater decline than APOE e4 carriers with low education, but the risk estimate was not statistically significant. Shadlen and colleagues[330] found that lower education was associated with greater cognitive decline among APOE e4 homozygotes but not among heterozygotes. Christensen and colleagues[331] found that among individuals with < 16 years education, those with at least one APOE e4 allele had greater cognitive decline on selected cognitive measures. This latter study did not control for baseline cognitive performance or age; it also reported many statistical comparisons without adjustment for multiple comparisons. The widely discrepant findings from these studies make it difficult to draw any conclusions about the interaction between education and APOE genotype in their association with cognitive decline.

The generally inconsistent findings reported by studies using categorical outcomes compared to those using continuous outcomes raises fundamental questions about the best methodological approach for examining this issue. The studies using categorical outcomes often categorize "cognitive decliners" as those who show the most pronounced decline. This may identify individuals who are in the prodromal stages of a progressive dementing disorder such as AD. In this case, it is possible that the association between years of education and cognitive decline reflects an underlying association between years of education and AD. Some additional methodological points might be considered. In the United States and some other developed countries, years of education may be a poor reflection of inherent ability for ethnic minorities and other groups for whom educational opportunities were not accessible. In the first half of the 20th century, when the participants in these studies were attending school, the quality of education in the United States differed across regions of the country and also across racial and ethnic groups. For these reasons, it has been suggested that reading skills, not years of education, may be a better marker of ability in these groups.[327]

In conclusion, the evidence is inconsistent regarding the putative association between years of education or its underlying construct and risk of cognitive decline. Further research is needed in this area that directly compares the association between years of education and cognitive decline using both categorical and non-categorical outcomes in the same sample.

Table 58. Years of education and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Alvardo, et al, 2002[322]	Community cohort (557)	4 years	Self-reported information about education in the following categories: 1) Illiterate 2) Literate (no formal education, can read and write) 3) 1 to 3 years of formal education 4) 4 or more years of formal education Then reclassified into 2 categories: 1) Incomplete primary school 2) Complete primary school	Change scores on a cognitive scale (0 to 32 points) Cognitive scale made up of simple tests of orientation, verbal memory, naming Categorized as: "Mild decline" = -2 to -7 "Severe decline" = -8 to -23 "Normal" = -1 to 12	Age Sex Educational level Baseline cognitive status Occupation	Less than primary education versus complete primary risk of cognitive decline: OR 1.49 (95% CI 0.92 to 2.43)
Koster, et al., 2005[323]	Community cohort (2088)	4 years	Self-reported education	Cognitive decline defined as ≥ 5-point decline on the 3MS from baseline to followup	Age Race Sex Educational level Baseline cognitive status Study site Household income Biomedical factors	Adjusted ORs (95% CI): Higher risk of cognitive decline associated with low education: > 12 years of education = reference 12 years education: OR 1.42 (1.10 to 1.83) < 12 years of education: OR 2.16 (1.59 to 2.94)
Lee, et al., 2006[324]	Community cohort (7118)	2 years	Self-reported education	Substantial cognitive decline defined as the worst 10% of the distribution of change on:	Age Clinical variables Smoking Physical activity	No differences by education for decline on composite cognitive score or verbal memory score. Higher educated less likely to show substantial cognitive decline on TICS

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
				1) TICS 2) Verbal fluency test 3) Verbal memory test 4) A composite score of all cognitive tests	Alcohol use	(p value trend = 0.0002) and verbal fluency (p value trend = 0.002); generally, those with the most and least education showed the largest effects. Intermediary education levels did not show a significant difference.
Lee, et al., 2003[325]	Community cohort (13,429)	2 years	Self-reported education	Substantial cognitive decline defined as the worst 10% of the distribution of change on: 1)TICS 2) Immediate or delayed recall of the TICS word list 3) Verbal fluency test 4) Verbal memory test 5) Digit span backwards 6) Composite score for all cognitive tests	Baseline test scores Age Clinical variables Medications Smoking Alcohol use BMI SF-36 vitality and mental health scores	Significant trends of decreasing odds of cognitive decline with increasing level of education for all tests (p value for trends ranged from < 0.01 to 0.03) On the composite cognitive score, compared to women with a RN diploma, lower risk of cognitive decline associated with: Graduate degree (OR 0.65, 95% CI 0.50 to 0.86) BS degree (OR 0.80, 95% CI 0.68 to 0.94)
Tyas, et al., 2007[183]	Community cohort (members of religious order) (470)	1 to 11 years	Self-reported education	Change from cognitively intact to MCI	Age Education APOE Prior cognitive state	Higher education associated with lower risk of incident MCI: Graduate degree = reference ≤ high school education: OR 2.36 (95% CI 1.26 to 4.42) Undergraduate degree: OR 1.53 (1.17 to 2.00)
Karla-mangla et al., 2009[329]	Community cohort (2353)	9 years	Self-reported education	Cognitive change on an abbreviated version of the TICS-m and on the word list memory sub-item	Baseline low performance Length of participation Imputed scores Age Sex Ethnicity	Education level was associated with baseline level of cognition but was not associated with rate of cognitive decline on either the total cognition score or the memory task score. These findings remained the same regardless of whether the association between education and cognitive change was assessed simultaneously with other SES

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
					Marital status Change in marital status Survivorship	variables or isolated from other SES variables. Among non-Mexican Hispanic Americans, each additional year of schooling was associated with a 0.35-point lower decline per decade (95% CI 0.05 to 0.65; P = 0.02) in recall score
Yaffe et al., 2009[258]	Community cohort (2509)	8 years	Self-reported education	Longitudinal performance on the 3MS Maintainers: Predicted slopes of 0 or greater (indicating no change or improvement in cognitive scores over time) Minor decliners: Predicted slopes less than 0 decline in cognitive score over time) but no more than one SD below the mean of the slopes Major decliners: Predicted slopes more than 1 SD below the mean	Age Race APOE genotype	When controlling for about 20 other factors associated with being a maintainer or decliner, risk of being a cognitive maintainer vs. a minor decliner for individuals with at least a high school education: OR 2.75 (95% CI 1.78 to 4.26) Risk of being a major decliner vs. a minor decliner: OR 0.52 (95% CI 0.37 to 0.73) Risk of being a cognitive maintainer vs. a minor decliner for individuals with at least a 9th grade literacy level: OR 4.85 (95% CI 3.00 to 7.87) Risk of being a major decliner vs. a minor decliner: OR 0.7 (95% CI 0.5 to 0.98)
Wilson et al., 2009[328]	Community cohort (6533)	6.5 (SD 3.6) years	Self-reported education	Composite measure of longitudinal change on the immediate and delayed recall of the East Boston Story, SDMT, and MMSE	Age Race Sex Five chronic medical conditions obtained from self-report of heart attack or MI, HTN, stroke, DM, and cancer	No linear association between education and rate of change in cognitive function Models that allowed for non-linearity in education and its relation to cognitive decline showed that education was associated with change in cognitive performance over time (coefficient >- 0.001; SE: < 0.001; p = 0.005). The rate of

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
						cognitive decline at average or high levels of education was slightly increased during earlier years of followup but slightly decreased in later years in comparison to low levels of education. Findings were similar among black and white participants.
Tervo, et al., 2004[267]	Community cohort (includes residents of nursing facilities)	3.26 (SD 0.7) years 66 MCI cases	Self-reported education	NINCDS-ADRDA DSM MCI criteria: CDR = 0.5 and performance on one memory test at least 0.5 SD below average	Age Race Sex Educational level Baseline cognitive status	Risk of incident MCI with a greater number of years of education: OR 0.80 (95% CI 0.71 to 0.90)
Christen-sen et al, 2008[331]	Community cohort (2551)	4 years	Self-reported education	Longitudinal change on word list memory task, MMSE, SDMT, Digit Span Backwards, reaction time task	Educational level Head Injury Premorbid intelligence	After controlling for cofactors, education was not associated with change scores in any of the cognitive tests Significant Interaction between APOE genotype and education for immediate (p = 0.04) and delayed word list recall (p = 0.008) such that among individuals with < 16 years education, those with at least one APOE e4 allele had greater cognitive decline.
Shadlen et al., 2005[330]	Clinical cohort – HMO (2140)	3.29 (SD 1.36) years	Self-reported education	Longitudinal change in CASI score	Age Race Sex Years of followup Depression Diabetes HTN	Education as a continuous measure was not associated with cognitive decline Lower education was associated with greater cognitive decline among APOE e4 homozygotes but not heterozygotes One e4 x education: coefficient 0.002 (95% CI -0.15 to 0.16; P =

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
					Cerebrovascular disease	0.976) Two e4 x education: coefficient 0.51 (0.12 to 0.91; P = 0.011)
Manly et al., 2005[327]	Community cohort (1362)	4.5 years	Self-reported education	Change on cognitive factors of memory, language and executive function Factor scores derived from multiple tests	Age Race Sex Educational level	After controlling for age, sex, race, and education, participants with lower literacy were more likely to have faster decline in cognition. Memory: β = 3.2; p = 0.002 Executive function: β= 1.0; p = 0.002 Language: β= 0.2; p = 0.000
Kalmijn et al., 1997[326]	Community cohort (718)	3 years	Self-reported education	Longitudinal change on the MMSE. Decline of at least 2 points categorized as cognitive decline.	Age Baseline cognitive function History of cardiovascular disease	Risk of cognitive decline compared to individuals with > 6 years of education: ≤ 6 years: OR 2.1 (95% CI 0.9 to 4.9) Compared to those with > 6 years of education: APOE e4 non-carrier (n = 272): ≤ 6 years: OR 3.1 (95% CI 1.1 to 8.8) APOE e4 carrier (n = 84): ≤ 6 years: OR 0.9 (95% CI 0.2 to 3.8) P = 0.10
Winnock et al., 2002[332]	Community cohort (626)	Range 1-8 years	Self-reported education	Longitudinal change on MMSE	Age Sex Education Time Age by time APOE	Decline on MMSE was not associated with education level (p = 0.14) There was no difference in rates of decline for APOE e4 carriers and non-carriers by education (p = 0.26)

Abbreviations: 3MS = Modified Mini-Mental State Examination; APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; BMI = body mass index; BS = Bachelor of Science degree; CASI = Cognitive Abilities Screening Instrument; CDR = Clinical Dementia Rating scale; CI = confidence interval; DM = diabetes

mellitus; DSM = Diagnostic and Statistical Manual of Mental Disorders; HMO = Health maintenance organization; HTN = hypertension; MCI = mild cognitive impairment; MI = myocardial infarction; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; RN = registered nurse; RR = relative risk; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SE = standard error; SES = socioeconomic status; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; TICS = Telephone Interview for Cognitive Status; TICS-m = Telephone Interview for Cognitive Status (modified version)

Occupation. We identified four eligible cohort studies in which the focus of the study was investigating the risk of cognitive decline and occupational history.[322,333-335] All of these studies had a continuous outcome; there were no eligible studies with categorical outcomes. The studies are summarized in Table 59; detailed evidence tables are provided in Appendix B. One of the studies used a community twin sample in the United States,[333] one used an HMO sample in the United States,[335] and two used community samples in Europe.[322,334] Length of followup ranged from 4 to 14 years. Exposure was determined based on self-reported information about occupation or job characteristics. Two studies used sample selection methods to minimize selection bias,[333,334] while the other two studies partially used such methods.[322,335] Definitions of cognitive decline varied among the studies and are described in Table 59. Analyses were appropriate and controlled for relevant potential confounders.

The four studies examined different aspects of jobs, making it difficult to compare results. One study examined the association between the number of hours worked each week and cognitive change over time;[334] another examined the association between job characteristics, such as general intellectual demand and physical exertion, and longitudinal cognitive performance;[333] the third study dichotomized occupation by farmers versus non-farmers to investigate the relation between jobs and cognitive decline;[322] and the fourth study assessed the association between three aspects of self-directed work (perceived autonomy, work control, and innovation) and cognitive decline.[335] The results from Alvarado and colleagues,[322] Potter and colleagues,[333] and Yu and colleagues[335] are broadly consistent. One showed a trend toward greater cognitive decline for farmers;[322] one reported that individuals who worked in jobs with high levels of physical exertion showed greater decline;[333] and the third reported that greater control over one's work is associated with better maintenance of cognition.[335] In all three studies, other factors, such as fewer years of education, actually accounted for more of the cognitive decline than did occupational characteristics. The study by Virtanen and colleagues[334] found that working longer hours, a characteristic of jobs associated with higher levels of education, was linked to greater decline on a test of reasoning. This finding makes the point that the impact of jobs may be multi-faceted, and further work needs to be done to examine the relation between different aspects of jobs and cognitive outcomes.

In conclusion, the data available currently suggest that the reported association between occupation and cognitive decline is largely attributable to level of education. In addition, further research is needed to decompose the various components of occupation and their role on late life cognition.

Table 59. Occupation and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Potter et al., 2006[333]	Community cohort (twin registry) (3880)	7 years	Self-reported occupation. Job characteristics coded based on Dictionary of Occupational Titles	Cognitive change on TICS-m from baseline to followup	Age Educational level Baseline cognitive status Twin pairing Medical conditions	Within twin pairs, jobs with higher general intellectual demands were associated with more improvement in cognitive function from baseline to followup (p = 0.011). Within twin pairs, jobs with higher physical exertion (p = 0.002) and higher visual attention (p = 0.023) were associated with greater cognitive decline. Within twin pairs, these occupational factors contributed little to cognitive change compared to the baseline cognitive score, the twin pairing, and educational level.
Alvarado et al., 2002[322]	Community cohort (557)	4 years	Self-reported occupational history. Lifelong occupation coded according to the Spanish National Classification of Occupations 5 categories: 1) White collar and skilled workers 2) Semi-skilled 3) Unskilled 4) Housewives 5) Farm workers	Change scores on a cognitive scale (0 to 32 points). Cognitive scale made up of simple tests of orientation, verbal memory, and naming. Categorized as: 1) “Mild decline” = -2 to -7 2) “Severe decline” = -8 to -23 3) “Normal” = -1 to 12	Age Sex Educational level Baseline cognitive status Occupation	Risk of cognitive decline for farm workers versus non-farm workers: OR 1.79 (95% CI 0.99 to 3.23) Less than primary and farm worker versus complete primary and non-farm worker: OR 2.36 (1.16 to 4.81) Less than primary and non-farm worker versus complete primary and non-farm worker: OR 1.39 (0.85 to 2.29)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
			Reclassified to: 1) Farm workers 2) Others			
Virtanen et al., 2009[334]	Community cohort (2214)	5 years	Self-reported responses to: "How many hours do you work per week in your main job including work brought home?" "How many hours do you work in an average week in your additional employment?"	Decline from baseline to followup on tests of memory, reasoning, vocabulary, phonemic verbal fluency, and semantic verbal fluency	Age Sex Educational level Marital status Followup employment status Occupational grade Income Physical health indicators Psychological stress Anxiety Sleep problems Health risk behaviors Social support Family stress Job strain	Compared to those who worked ≤ 40 hours/week, those who worked: 41 to 55 hours/week declined more on reasoning test (mean difference -2.23; SE = 0.37; p = 0.046) > 55 hours/week declined more on reasoning test (mean difference -2.9; SE = 0.49; p = 0.007) Test for linear trend, p = 0.036
Yu et al., 2009[335]	Clinical cohort – HMO (626)	14 years	Self-reported information on self-directed work. Included three components and was operationalized in three ways as perceived autonomy, work control, and innovation as measured by a scale of the Work Environment Inventory	Longitudinal performance on: Measures of verbal memory: (a) Word fluency (b) Immediate recall (c) Delayed recall Measures of inductive reasoning: (a) PMA reasoning measure	Age Sex Educational level Income	Jobs with high levels of work control were associated with better maintenance of cognition over time Every increased unit of work control was associated with a 0.13 increase in verbal memory ($p < 0.05$) Every increased unit of work control was associated with a 0.14 t-score unit increase in inductive reasoning ($p < 0.05$

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
				(b) ADEPT Letter Series test (c) Word series and (d) Educational Testing Service number series		

Abbreviations: ADEPT = Adult Development and Enrichment Project; CI = confidence interval; HMO = health maintenance organization; OR = odds ratio; PMA = Primary Mental Abilities; RR = relative risk; SD = standard deviation; SE = standard error; TICS-m = Telephone Interview for Cognitive Status (modified version)

Social engagement. We identified 15 cohort studies that examined the association between social engagement and the development of MCI or cognitive decline.[188,190,258,271,321,329,336-344] These studies are summarized in Table 60; detailed evidence tables are presented in Appendix B. Social engagement as a risk factor was described by different exposures in the studies, including objective measures such as marital status, living situation, number of people in social network, as well as subjective measures such as feelings of loneliness and perceptions of social support. Engaging in social activities (which may or may not involve social engagement) is mostly covered in the sections on cognitive engagement and leisure activities, although some overlap is unavoidable given that the boundaries are sometimes nebulous. Although 15 social engagement studies were identified, the measurement of exposure and reporting of outcomes varied among the studies. Hence, they were not combined to provide a single summary statistic; rather, qualitative descriptions of the studies are provided in this discussion.

Qualitatively, the measurement of exposures in the studies fall under three main categories: social network size, social support, and marital status. Ten of the 15 studies were conducted in various regions of the United States,[188,190,258,271,321,329,336-339] four in Europe,[340,341,343,344] and one in Hong Kong.[342] Ten studies reported continuous outcomes of cognitive decline.[188,271,329,336-341,344] The other five reported decline as a categorical outcome, although the definition varied from study to study.[190,258,321,342,343] All studies used community samples and attempted to decrease selection bias. Some studies did not exclude individuals who were cognitively impaired at baseline[336,338,340] and therefore could have included some demented individuals, except Green et al.,[338] where the mean age at baseline was 47.3. Though all other studies attempted to exclude those who were cognitively impaired at baseline, the criteria and methods of screening were heterogenous and included: 3MS > 80;[258] MMSE > 24;[341] MMSE > 28;[337] and participants scoring in the top third of the screening test.[339] The other studies had a broad inclusion criteria of simply non demented. Some studies had a significant amount of loss to followup (> 50 percent).[337,338,344] One study[338] was a continuation of another.[337] The average length of followup ranged from 2 to 21 years. Measurement of social engagement was done through self-report in all the studies. There was no objective validation of the measure for ascertaining exposure in any of the studies. Five studies compared baseline characteristics between the exposed and unexposed groups.[190,258,321,340,341] Some studies compared the baseline characteristics of the participants who were followed up compared to those who were lost to followup and found statistically significant differences between the two groups; for example, participants who were followed up were younger and more educated than those who were not.[337,338] One study used informant interviews;[339] however, this was mainly to collect proxy information for missing data. The methods used to define cases and cognitive decline are described in Table 60. None of the studies reported a priori power calculations. The analyses were largely appropriate with adequate adjustment for confounders.

Of the 15 studies, five examined the relationship between social network and cognitive decline. Two studies concluded that a larger social network decreased cognitive decline.[336,337] However, continued followup of one of these cohorts[337] found discrepant results in that there was no association between social network size or support and cognitive decline.[338] However, of the 2607 participants in the original study, only 874 were in the followup study, and they differed in demographic characteristics from the original cohort. This may explain the difference in findings between the two studies. In another study, there was no association between the size of the social network and cognitive decline; however, decreased social engagement as measured by group memberships was associated with an increased risk of cognitive decline (OR 2.92; 95 percent CI

1.35 to 6.36).[343] In a study examining characteristics of a social network, men of Japanese descent living in the United States and having current friends who were Japanese were at lower risk of cognitive decline (OR 0.64; 95% CI 0.44 to 0.93).[321]

Four studies examined the relationship between social support and cognitive decline. One found that lack of social support increased the risk of cognitive decline (OR 1.2; 95 percent CI 1.01 to 1.43),[271] while another found an increased risk in men but not women in a preliminary model, which then became non-significant in an adjusted model.[342] In the third study, lack of social support was measured as loneliness, which was found to be associated with more rapid decline in global cognition, semantic memory, perceptual speed, and visuospatial ability.[188] In another study, participants who reported having enough social support had a lower risk of becoming a major cognitive decliner.[258] Perception of social support in a high functioning group was examined only in one study and was not found to be significantly associated with cognitive decline in a fully adjusted model.[339]

Six studies examined the relationship between marital status and cognitive decline.[190,329,340-342,344] Loss of spouse was a significant risk factor for cognitive decline in three studies.[190,329,340] Of these, only one defined MCI as a categorical diagnosis using published criteria; investigators found that being widowed (OR 3.30; 95 percent CI 1.6 to 6.9) and being without a partner (OR 2.14; 1.2 to 3.8) at midlife were both associated with increased risk of MCI.[190] However, two other studies did not report a significant association between cognitive decline and marital status[341,344] or living situation.[341] The final study[342] reported that greater cognitive decline was associated with being divorced in males, but the association was not found in single or widowed males or in females. Given the latter findings, and the extremely broad confidence intervals for the association between divorced males and cognitive decline, the robustness of the finding that greater cognitive decline in males is associated with being divorced is questionable. The association between living with someone and cognitive decline was inconsistent across studies. One study showed no significant association,[258] while two other studies found that those who lived alone at baseline and followup had an increased risk of cognitive decline.[190,341]

In conclusion, although comparison across studies is difficult given the different measures of exposure, it is evident that results are inconsistent among the studies on social network size and social support. In addition, those studies reporting a beneficial association between measures of social engagement and maintenance of cognition generally report relatively small effect sizes, suggesting that residual confounding may explain the association. Thus, there is currently not sufficient evidence supporting a protective effect of social engagement. However, there appears to be a more robust association between the loss of a spouse and cognitive decline as evidenced by the findings from three studies. The findings are inconsistent regarding living alone or being without a partner for any reason. We suggest that some of the heterogeneity in the findings may be attributed to the shorter followup time in some studies in which the majority of the data was collected in late life; as the two studies with over 15 years of follow up showed that those who were single at baseline and followup were at increased risk of cognitive decline.

Table 60. Social engagement and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Barnes et al., 2004[336]	Community cohort (6158)	6 years (mean)	Social network Social engagement (scale 0 to 8 points)	Episodic memory: Immediate and delayed recall of 12 ideas contained in the East Boston Story Perceptual speed: SDMT Global cognition: MMSE	Age Race Sex Marital status Educational level Income	0.002 unit reduction in cognitive decline for every point on social network ($p < 0.001$) 0.009 unit reduction of cognitive decline for every point on the social engagement scale ($p < 0.001$)
Holtzman et al., 2004[337]	Community cohort (881; 354 included in the longitudinal analysis)	12.4 years (mean)	Social network Emotional support	MMSE	Change in physical disability Change in dysphoria MMSE at baseline Lifetime presence of alcohol disorder Cerebrovascular disease status Age Sex Race Education level	Linear effect of social network on MMSE: SE = 0.06; $\beta = 0.14$; $p < 0.01$ Effect size = 0.06; $p = 0.006$
Green et al., 2008[338]	Community cohort (2607)	10.9 years (mean)	Network size Frequency of interaction	MMSE	Age Race Sex Educational level Past year household income Depressive symptomatology Lifetime alcohol use disorder Ability to perform ADLs Cerebrovascular disease Baseline cognitive status	Change in MMSE was not significantly affected by: Network size: $\beta = 0.028$ (-0.037 to 0.093); $p = 0.403$ Frequency of contact: $\beta = 0.002$ (-0.073 to 0.078); $p = 0.950$ Emotional support: $\beta = -0.004$ (-0.047 to 0.040); $p = 0.862$ Composite social network: $\beta = 0.005$ (-0.023 to 0.033); $p = 0.721$
Barnes et al., 2007[271]	Community cohort	10 years (median)	Social support	Modified MMSE	Age Education	Adjusted OR for lack of social support: 1.20 (95% CI 1.01 to

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
	(9704)				Baseline cognitive function Study site	1.43)
Seeman et al., 2001[339]	Community cohort (1189)	7.4 years (mean)	Perception of social support network	Language :18 item Boston Naming test Abstraction: 4 items from the Wechsler's Adult intelligence scale Spatial ability: Copying image Incidental recall of confrontation naming Delayed recall of a story	Race Sex Educational level Income Number of reported chronic illnesses Pulmonary function Amount of strenuous leisure activity Amount of strenuous yard/house maintenance Depressive symptoms Self-efficacy beliefs	After controlling for covariates, greater baseline social support was a predictor of cognitive function on 7.5-year followup: beta = 1.26; p = 0.07. When the model was reduced by excluding baseline cognitive status and other sociodemographic factors, the relationship became significant; beta = 1.20; p = 0.05
Wilson et al., 2007[188] Rush Memory Aging Project	Community cohort (1023; 857 after exclusions)	Mean 3.3 years Range 2 to 5 years 76 AD cases	Loneliness by self-report (questionnaire)	MMSE 7 measures of episodic memory: Immediate and delayed recall of Logical Memory Story and of the East Boston Story, plus Word List Memory, Word List Recall, and Word List Recognition 3 tests of semantic Memory: Verbal Fluency Test and short forms of the Boston Naming Test and the National Adult reading Test 3 working memory tests including Digit Span	Age Sex Level of educational achievement	Global cognition – Loneliness x time: Beta Estimate (SE): 0.01 (0.01); p = 0.03 Episodic memory – Loneliness x time: Beta Estimate (SE) 0.00 (0.01); p = 0.79 Semantic memory – Loneliness x time: Beta Estimate (SE) −0.02 (0.01); p = 0.01 Working memory – Loneliness x time: Beta Estimate (SE) -0.02 (0.01); p = 0.09 Perceptual speed – Loneliness x time: Beta Estimate (SE) -0.02 (0.01); p = 0.03 Visuospatial ability – Loneliness x time: Beta Estimate (SE) -0.03 (0.01); p = 0.04

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
				Forward and Backward plus Digit Ordering 4 measures of perceptual speed including Number Comparison, Symbol Digit Modalities Test (oral version), and 2 indexes from a modified Stroop Neuropsychological Screening Test 2 visuospatial tests including a 15-item version of Judgment of Line Orientation and a 17-item version of Standard Progressive Matrices		
Aartsen et al., 2005[340]	Community cohort (1144)	6 years	Loss of spouse	Recall of 15 words from the Auditory Verbal Learning Test	Age Sex Educational level Physical health at baseline Mental health at baseline	Statistically significant difference between widowed and non-widowed men: $\chi^2 = 6.6$; $p < 0.05$ but not for women: $\chi^2 = 2.3$; $p = 0.13$.
Van Gelder et al., 2006[341]	Community cohort (2285; 1734 alive at first followup)	15 years	Marital status Living situation	MMSE	Age Education Country Smoking Alcohol consumption Prevalence of MI, stroke, diabetes, and cancer Living situation Baseline cognitive functioning For analysis of living situation,	No significant difference in rate of cognitive decline over the 10-year followup for the three groups defined by marital status: 1) Married from 1985-90: decline of 1.1 points (95% CI 0.9 to1.4) 2) Married in 1985 but unmarried in 1990 had additional decline of 1.0 point (0.1to 1.9) 3) Unmarried in 1985 and 1990 had an additional decline of 1.3 points (0.5 to 2.1)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
					marital status was included as a covariate	No significant difference in rate of decline over the 10-year followup for the three groups defined by living situation: 1) Lived with others in 1985 and 1990 had a cognitive decline of 1.1 points (95% CI 0.8 to 1.4) 2) Lived with others in 1985 but alone in 1990 had an additional decline of 1.1 points (-0.2 to 2.0) 3) Alone in 1985 and 1990 had an additional cognitive decline of 2.7 points (1.7 to 3.7)
Ho et al., 2001[342]	Community cohort (1200)	3 years	Social support score	Information and orientation part of Clifton Assessment procedure for the elderly	Age Education	Initial model: Marital status divorced vs. married: OR for men: 12.0 (95% CI 1.1 to 134.8) OR for women: 3.8 (0.6 to 25.1) Social support score < 9: OR for men: 2.8 (95% CI 1.1 to 6.7) OR for women: 1.2 (0.6 to 2.2)
Muniz-Terrera et al., 2009[344]	Community cohort (2053)	9 years	Marital status	MMSE	Age Sex Educational level Profession Marital status Baseline MMSE	Rate of decline of MMSE in married versus unmarried 0.01 (SE = 0.05; P > 0.05)
Karla-mangla et al., 2009[329]	Community cohort (6476)	9 years	Marital status	TICS for participants aged ≤ 79 years, and in-person interviews for participants older than 79 years	Cognition at baseline Length of participation Age Gender Ethnicity	Association with the slope of total cognition (per decade): Married = reference Widow/widower: -0.79 (-1.50 to -0.08) Separated/divorced: 0.71 (-0.58

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
					Education Wealth and income at baseline	to 2.00) Never married: -1.00 (-2.82 to -0.81) Association with the slope of recall (per decade): Married = reference Widow/widower: -0.64 (-1.15 to -0.13) Separated/divorced: 0.62 (-0.33 to 1.56) Never married: - 1.42 (-2.58 to -0.27)
Hakansson et al., 2009[190]	Community cohort (1449)	Average 21 years.	Marital status (married/ cohabiting, single, or divorced)	MMSE and NINCDS-ARDA	Age Sex Educational level Baseline cognitive status BMI APOE Systolic BP Region of residence Smoking Occupation Physical activity at work Depression at mid-life	Risk of MCI (78/1250) Status at mid-life OR (95% CI): Without partner: 2.14 (1.2 to 3.8) Widowed: 3.30 (1.6 to 6.9) Single/divorced: 1.50 (0.7 to3.4)
Graves et al., 1999[321]	Community cohort (1836; 1604 analyzed)	2 years (exposure lifelong)	Past and current friends	Cognitive decline defined as mean change of -1 SD, i.e., > 5.15 points loss in 2 years	Age Sex Educational level Baseline cognitive status Followup time	Having current friends was associated with lower odds of decline. Current friends mostly Japanese: OR 0.64, 95% CI 0.44 to 0.93; p < 0.01 Past friends mostly Japanese: OR 0.91; 95% CI 0.63 to 1.33

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Zunzu-negui et al., 2003[343]	Community cohort (964; 557 analyzed)	4 years	Social network Social integration Social engagement	Cognitive decline on composite measure of cognitive tests. Severe decline defined as greater than 1 SD below the mean change. Mild decline defined as a change within 1 SD of the mean change.	Age Educational level Sex Baseline cognitive status Depression BP Functional limitations	OR for severe cognitive decline (95% CI): No group membership in men: 2.92 (1.35 to 6.36) Social engagement with children in men: 0.88 (0.78 to 1.00) Less social engagement with friends in women: 0.77 (0.59 to 1.00)
Yaffe et al., 2009[258]	Community cohort (2509)	8 years	Social support Living with someone	3 MS Participants with predicted slopes of the 3MS scores of ≤ 0 were considered maintainers; > 0 but no more than 1 SD below the mean were considered minor decliners; ≥ 1 SD below the mean were considered major decliners.	Age Race Educational level APOE genotype	Those who had enough social support had lower risk of cognitive decline (OR [95% CI)]: Maintainer vs. minor decliner: 0.94 (0.73 to 1.21) Major vs. minor decliner: 0.69 (0.51 to 0.91) Living with someone was not significantly associated with cognitive decline. Maintainer vs. minor decliner: 1.24 (0.98 to 1.57) Major vs. minor decliner: 1.00 (0.75 to 1.34)

Abbreviations: 3MS = Modified Mini-Mental State Examination; AD = Alzheimer's disease; ADLs = activities of daily living; APOE = apolipoprotein E gene; CI = confidence interval; MI = myocardial infarction; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR = odds ratio; SDMT = Symbol Digit Modalities Test; SD = standard deviation; SE = standard error; TICS = Telephone Interview for Cognitive Status

Cognitive engagement. We identified four eligible cohort studies that examined the association between cognitive engagement and development of MCI or cognitive decline.[335,345-347] These studies are summarized in Table 61; detailed evidence tables are in Appendix B. One of the studies reported a categorical outcome,[345] and the other three reported continuous outcomes of cognitive decline.[335,346,347] Given the small number of eligible studies, the studies reporting continuous outcomes are included in this discussion. Two of the studies used community samples in the United States,[345,346] one used a sample from a health maintenance organization (HMO) in the United States,[335] and the fourth used a clinical sample in Europe.[347] The length of followup averaged 3 to 14 years. Two of the studies used sample selection methods to minimize selection bias,[346,347] while the remaining studies partially used such methods.[335,345] In two of the studies, the participants were non-demented at baseline;[345,347] the other two studies appeared to include all participants at baseline regardless of cognitive status, but given the length of the followup periods, it is assumed here that few participants were demented at baseline.[335,346] All of the studies used self-report of the frequency of current involvement in specific activities. There was no objective validation of the method for measuring exposure, but one study[194] did ask an informant to confirm the participant's report of involvement in activities. The studies did not compare baseline characteristics between those exposed and unexposed, but one study compared baseline differences between individuals who developed amnestic MCI and those who did not.[345] The case definitions and cognitive outcomes used are described in Table 61. The analyses appear generally appropriate and controlled for relevant potential confounders, but none of the studies conducted a priori sample size calculations.

One study[345] reported an attenuation of risk of amnestic MCI with increasing frequency of cognitive activities; another study[346] reported a reduction in a global measure of cognitive decline with increasing levels of cognitive activity; and the third study[347] reported that cognitively engaging activity was associated with less cognitive decline on selected cognitive measures. In contrast to these findings, Yu and colleagues reported no association between cognitive decline and involvement in cognitive leisure activities.[335] Their study report did not detail the activities included in the cognitive activity group, nor did it provide any specific results on the cognitive activity analyses. This limits our ability to identify differences among the studies that may contribute to the discrepant results.

In conclusion, there is limited but inconsistent evidence suggesting that increased involvement in cognitive activities in later life is associated with less cognitive decline and lower risk of incident amnestic MCI. In addition to the limited information reported in one study and noted above, there are some other challenges to interpreting these results. First, the effect sizes are relatively small and limited to selective measures in some studies. It is possible that residual confounding may contribute to some of the findings. Second, given the long subclinical prodromal phase of AD, it is not possible to determine whether less involvement in cognitive activities in some individuals is an early symptom of AD. Third, validation of the type and extent of exposure is needed.

Table 61. Cognitive activities and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Verghese et al., 2006[345]	Community cohort (437)	5.6 years (4.1) (mean [SD])	Self-report of frequency of current involvement in the following activities: reading books or newspapers, writing for pleasure, doing crossword puzzles, playing board games or cards, participating in organized group discussions, and playing musical instruments	Criteria for amnestic MCI: 1) Does not meet criteria for dementia; 2) Objective memory impairment based on cognitive testing; 3) Subjective report of memory symptoms; 4) Normal general cognitive functioning; 5) Generally preserved activities of daily living.	Age Sex Educational level Chronic illnesses Participation in other leisure activities	Risk of developing aMCI with each 1-point increment (on a 42-point scale) in the cognitive activity score: HR 0.95 (95% CI 0.91 to 0.99) None of the individual cognitive activities (adjusted for participation in other activities) showed independent associations with lower risk of aMCI in the fully adjusted models.
Wilson et al., 2003[346]	Community cohort (4392)	5.3 years	Self-report of current involvement in the following activities: viewing television; listening to radio; reading newspapers; reading magazines; reading books; playing games like cards, checkers, crosswords, or other puzzles; and going to a museum	Global composite index of scores on the MMSE, the immediate and delayed recall of the East Boston Story, and the oral version of the Symbol Digit Modalities Test	Age Race Sex Educational level	Frequency of cognitive activity was associated with a reduction of 0.012 (SE 0.003) units in cognitive decline ($p = 0.001$). This is equivalent to about 19% less decline for each point on a 5-point cognitive activity scale.
Bosma et al., 2002[347]	Clinical cohort – family practice clinics (830)	3 years	Self report of activities described as “mentally active sports (e.g., chess, puzzles)”	Longitudinal performance on the following cognitive measures: Stroop Color-Word Test , word list memory test, a letter-digit substitution test, semantic verbal fluency test, and the MMSE	Age Sex Educational level Baseline cognitive status Length of followup interval	At least 1 hour per week in mentally active sports was associated with less cognitive decline on the MMSE (β coefficient 0.40; $p < 0.01$); letter-digit substitution test ($\beta = 1.18$; $p < 0.01$). No difference in longitudinal performance was observed on the other tests.

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Yu et al., 2009[335]	Clinical cohort – HMO (626)	14 years	Self-report on the socializing, educational, and cultural items on the Life Complexity Inventory Proportion of time spent weekly in cognitive activities divided by time spent in all leisure activities	Longitudinal performance on: Measures of verbal memory: (a) Word fluency (b) Immediate recall (c) Delayed recall Measures of inductive reasoning: (a) PMA reasoning measure (b) ADEPT Letter Series test (c) Word series and (d) Educational Testing Service number series	Age Sex Educational level Income	Involvement in cognitive leisure activities was not associated with longitudinal performance on either the memory or inductive reasoning tasks. Specific results were not provided in the manuscript.

Abbreviations: ADEPT = Adult Development and Enrichment Project; aMCI = amnestic mild cognitive impairment; CI = confidence interval; HMO = health maintenance organization; HR = hazard ratio; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PMA = Primary Mental Abilities; SD = standard deviation; SE = standard error

Physical activities. We identified eight eligible cohort studies that examined the association between physical activity and development of MCI or cognitive decline.[199,258,261,342,345,348-350] These studies are summarized in Table 62; detailed evidence tables are in Appendix B. Seven studies had a categorical outcome; the eighth had a continuous outcome, but we have included it here because it focused on a select subgroup of individuals (women with diabetes) relevant to one of the key questions of this systematic review.[261] These eight studies are the focus of attention in what follows. There were an additional three studies with continuous outcomes of cognitive decline[335,347,351] which are not reviewed in detail, but for which we report general conclusions. Five of the studies used community samples in the United States,[258,261,345,348,350] and one study each used community samples in Canada,[199] Europe,[349] and Hong Kong.[342] The length of followup ranged from 2 to 8 years. The cognitive status of participants at baseline differed among the studies. Two studies[348,349] may have included some individuals with dementia at baseline, as they did not appear to apply exclusionary criteria regarding impaired cognitive function. Other studies[258,350] attempted to exclude those with dementia by only including individuals who scored above 80 points on the 3MS or at least 23 out of 26 points on an abbreviated MMSE test. One study[342] excluded participants categorized at baseline as having cognitive impairment based on performance on 12 items of an orientation and information test. For the remaining three studies,[199,261,345] participants were non-demented at baseline, with a subset of the individuals specifically having MCI in one study,[345] and a subset of individuals being cognitively normal in some studies.[199,345] Seven studies used sample selection methods to minimize selection bias,[199,258,261,342,348-350] and the other partially used such methods.[345] All studies used self-reported information on involvement in physical activities at baseline; some asked about specific activities, but the majority asked more general questions about any physical activities. Since a number of the studies used open-ended questions to obtain information about engagement in physical activities, it was difficult to assess the degree of overlap among the activities across studies. Only one study provided some information on the reliability and validity of the physical activity questions.[349] Five studies compared baseline characteristics between those exposed and unexposed.[258,261,348-350] The case definitions for the studies are described in Table 62. The analyses appear generally appropriate and most controlled for relevant potential confounders. However, one study[342] defined a case by a threshold score on the cognitive measure, but in the analysis did not control for performance on the cognitive measure at baseline. This may have markedly influenced their results since a large proportion of the females, compared to the males, scored just above this threshold at baseline. None of the studies reported a priori sample size calculations.

For all studies, the risk estimates were typically in the hypothesized direction, and there was often a dose-response pattern for the association between more physical activity and the various case definitions of cognitive decline. However, when statistical significance was considered, the results were inconsistent. Five studies reported that more physical activity was associated with a lower risk of CIND, cognitive impairment, or cognitive decline,[199,258,342,348,350] but in two of these studies the benefit was attributed entirely to a significant effect among females,[199,342] and in one the entire sample was female.[350] Devore and colleagues[261] found that among women with diabetes those in the highest tertile level of physical activity showed less cognitive decline compared to those in the lowest tertile level of physical activity. The difference in longitudinal change between the two groups was small, and when the model included adjustment for physical disability the results were no longer statistically significant. The last two studies[345,349] found no significant association between levels of physical activity and risk of either amnestic MCI or

cognitive decline. These two studies had the smallest sample sizes, which suggests that lack of statistical power may have been an issue. One of these studies[349] found that among carriers of the APOE e4 allele, physical activity showed significant protective benefit against cognitive decline.

The three studies that had continuous outcome variables also reported inconsistent results. Weuve and colleagues[351] showed that increased levels of physical activity were associated with better long-term performance on multiple cognitive tests, but Bosma and colleagues[347] showed that physical activity was associated with less decline on only one of a number of cognitive tests. In contrast, Yu and colleagues[335] showed no association between physical activity and cognitive decline.

The inconsistent findings may be due to a number of factors, including small number of cases and heterogeneity in both the types and quality of the exposure and outcome measures.

In conclusion, the data currently available provide preliminary evidence for a beneficial effect of physical activity deterring cognitive decline, but overall the results are not robust. Further work using standardized methods to assess exposure is needed to confirm these findings and draw firmer conclusions.

Table 62. Physical activity and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Ho et al., 2001[342]	Community cohort (988)	3 years 139 incident cognitive impairment	Self-report of whether individual exercised (no other details)	Incident cognitive impairment defined as a score over < 8 points on the Clifton Assessment Procedure for the Elderly	Age Sex* Educational level *Final model adjusted only for sex	Adjusted OR (95% CI) for incident cognitive impairment for exercise "no" versus "yes": Entire group: 2.1 (1.3 to 3.3) Females: 2.2 (1.2 to 3.8) Results not significant for males, but no specific results provided.
Laurin et al., 2001[199]	Community cohort (4615)	5 years 436 incident CIND; 882 incident cognitive loss	Self-report responses to two questions about frequency and intensity of exercise for individuals who reported physical activity Composite physical activity score categorized: 1) "Low" = less than weekly 2) "Moderate" = weekly 3) "High"= ≥ 3 times/week	Incident CIND as defined by the Canadian Study of Health and Aging or cognitive loss defined as > 4 point decline on the 3MS at followup	Sex Educational level Family history of dementia Tobacco use Alcohol use NSAID use Daily living activities Clinical variables	Adjusted OR (95% CI) for CIND compared to no physical activity: For men: Low activity: 0.65(0.30 to 1.38) Moderate activity: 0.84 (0.53 to 1.34) High activity: 0.68 (0.39 to 1.20) p = 0.24 For women: Low activity: 0.69 (0.41 to 1.16) Moderate activity: 0.55 (0.36 to 0.82) High activity: 0.47 (0.25 to 0.90) p =0.003 Adjusted OR (adjusted for age and education, with 95% CI) for cognitive loss compared to no physical activity: For men: Low activity: 0.96 (0.63 to1.44) Moderate: 0.85 (0.63 to 1.15) High: 0.98 (0.71 to1.35) For women:

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
						Low: 1.06 (0.78 to1.45) Moderate: 0.92 (0.72 to 1.17) High: 0.58 (0.40 to 0.82)
Lytle et al., 2004[348] MoVIES study	Community cohort (929)	2 years 110 incident cognitive decline	Self-report responses to question about whether individual engaged in an exercise program, and, if so, what type of exercise, exercise equipment used, and frequency and duration of exercise Categorized exercise as aerobic versus non-aerobic, then categorized by frequency, as follows: High activity = aerobic activity ≥ 30 minutes at least 3 days/week. For some analyses high activity defined as ≥ 30 minutes at least 5 days/week Low activity = all other exercise	Cognitive decline defined as ≥ 3-point decline on the MMSE	Age Sex Educational level Baseline cognitive score Self-rating of health	Adjusted OR (95% CI) for cognitive decline compared to "no exercise": High activity (3 days/week): 0.39 (0.19 to 0.78) Low activity: 0.69 (0.43 to 1.10). When high activity defined as 5 days/week, it was still significant, but the low activity was also significant using this threshold.
Schuit et al., 2001[349]	Community cohort (primarily community but only 88% lived indepen-dently at home) (347)	3 years	Self-report responses to questions about the frequency and duration of walking and bicycling in the previous week, the average amount of time spent weekly on hobbies and gardening in both summer and winter; and the average amount of	Cognitive decline defined as a decrease of > points on the MMSE	Age Sex Educational level Smoking Alcohol Baseline cognitive function Clinical variables Disabilities in ADL Health status	Adjusted OR (95% CI) for cognitive decline, with > 60 minutes/day as the reference: < 30 min/day: 2.0 (0.7 to 5.6) 31 to 60 min/day: 1.8 (0.6 to 5.1) There was an interaction of physical activity and APOE with cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
			time spent monthly on odd jobs and sport Summed score for total weekly activity categorized: 1) ≤ 30 min/day 2) 31 to 60 min/day 3) > 60 min/day			The OR of cognitive decline among inactive carriers of the APOE allele (3.7; 95% CI 1.1 to 12.6) was nearly 4 times the OR of active carriers
Verghese et al., 2006[345]	Community cohort (488) 58 amnestic MCI	Mean 5.6 years (SD 4.1)	Self-report of frequency of involvement in the following 11 physical activities: Playing tennis or golf, swimming, bicycling, dancing, participating in group exercises, playing team games such as bowling, walking for exercise, climbing more than two flights of stairs, and babysitting Frequency of participation reported as "daily," "several days per week," "once weekly," "monthly," "occasionally," or "never." Responses used to create index: 7 points for daily participation; 4 points for participating several days per week; 1 point for participating once weekly; and 0 points for participating monthly, occasionally, or never. Summed the	Criteria for amnestic mild cognitive impairment (aMCI): 1) No dementia 2) Memory impairment 3) Memory symptoms 4) Normal cognitive function (verbal IQ >84 and score of less than 8 on the Blessed test) 5) Generally preserved activities of daily living	Age Sex Educational level Chronic illnesses Participation in other leisure activities	A 1-point increment in physical activity score was not associated with an increased risk of aMCI (adjusted HR = 0.970) Compared to physical score < 8 points, adjusted HR for 8 to 14 points: 0.920 (0.520 to 1.629) For > 14 points: 0.493 (0.227 to 1.072)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
			activity-days for each activity to generate a physical-activity score, ranging from 0 to 70. Responses dichotomized as "rare participation" (once a week or less) versus "frequent participation" (several days a week or more).			
Yaffe et al., 2001[350]	Community cohort (5925)	Mean 7.5 years	Self-reported physical activity determined by the number of city blocks individual walked daily for exercise or as part of normal routine, the number of flights of stairs climbed daily, and responses on the modified Paffenbarger Scale. Activities classified as low (walking or gardening), medium (dancing or tennis), or high (jogging or skiing) intensity. Total kilocalories expended calculated	Cognitive decline defined as a change of ≥ 3 points on an abbreviated MMSE over period of followup	Age Educational level Health status Functional limitation Depression score Stroke Diabetes Hypertension Myocardial infarction Smoking Estrogen use	Risk of cognitive decline compared to lowest quartile of blocks walked per week as reference (OR [95% CI]): Second quartile: 0.87 (0.72 to 1.05) Third quartile: 0.63 (0.52 to 0.77) Highest quartile: 0.66 (0.54 to 0.82) Risk of cognitive decline compared to lowest quartile of total kilocalories per week as reference (OR [95% CI]): Second quartile: 0.90 (0.74 to 1.09) Third quartile: 0.78 (0.64 to 0.96) Highest quartile: 0.74 (0.60 to 0.90)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Yaffe et al., 2009[258]	Community cohort (2509)	8 years	Self-reported information on weekly moderate/vigorous exercise, defined as engagement in moderate to vigorous exercise and activity (e.g., aerobics, weight training, or brisk walking) at least once a week	Longitudinal performance on the 3MS Maintainers: Predicted slopes of 0 or greater (indicating no change or improvement in cognitive scores over time) Minor decliners: Predicted slopes less than 0 decline in cognitive score over time) but no more than one SD below the mean of the slopes Major decliners: Predicted slopes more than 1 SD below the mean	Age Race Educational level APOE genotype	When controlling for about 20 other factors associated with being a maintainer or decliner, risk of being a cognitive maintainer vs. a minor decliner for: Weekly moderate/vigorous exercise: OR 1.31(95% CI 1.06 to 1.62). Risk of being a major decliner vs. a minor decliner: OR 0.97 (95% CI 0.73 to 1.28)
Devore et al., 2009[261]	Community cohort (1550) All had diabetes	4 years	Self-reports of average amount of time per week spent in the following activities during the past year: Running (< 10 minutes/mile); jogging (> 10 minutes/mile); walking or hiking outdoors; racquet sports; lap swimming; bicycling; aerobic dancing or use of exercise machines; other vigorous activities (e.g., lawn mowing); and low-intensity exercise (e.g.,	Longitudinal performance on six cognitive tests used to create general cognition index and memory index. Tests were: TICS, East Boston Memory Test, Category Fluency, word list memory, and Digit Span backward.	Age Education, Baseline cognitive status Disability indicators (osteoarthritis, chronic bronchitis, fatigue, balance problems, moderate-to-severe body pain, and limitations in walking)	Among women with diabetes greater levels of long-term physical activity were associated with less decline on all cognitive measures over about 2 years in models adjusting for age and education. Mean difference on global score between extreme tertiles of activity was 0.09 standard units (95% CI 0.02 to 0.16; P value for trend = 0.02). Adjustment for disability factors reduced the magnitude of associations for all measures and they were no longer significant. Mean difference in global score comparing the highest tertile with the lowest was 0.04 standard units (95% CI 0.03 to 0.12; P value for trend = 0.2).

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
			yoga, stretching, toning)			Increased levels of walking were not associated with cognitive decline; comparing extreme tertiles of the global score, mean difference = 0.01, 95% CI 0.09 to 0.06; P value for trend = 0.8).

Abbreviations: 3MS = Modified Mini-Mental State Examination; ADL = activities of daily living; aMCI = amnestic mild cognitive impairment; APOE = apolipoprotein E gene; CI = confidence interval; CIND = cognitive impairment not demented; HR = hazard ratio; IQ = intelligence quotient; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; SD = standard deviation; TICS = Telephone Interview for Cognitive Status

Other leisure activities. We identified two eligible cohort studies that examined the association between non-physical leisure activities and cognitive decline.[336,347] Both studies defined the activities as "social" activities. We also identified one cohort study that examined the association between a range of leisure activities – including those considered to be social, productive, and physical – and cognitive decline.[352] Two of the studies included "leisure employment, or part- or full-time work" in the list of leisure activities. Although work is not typically considered a leisure activity, these studies best fit in the present section. The leisure activities assessed for each study are listed in Table 63. Some of the leisure activities in these studies overlapped with some of the activities considered to be "cognitively engaging" in other studies, so the results described here should be interpreted in conjunction with the findings for Question 2 for the "Cognitive Engagement" factor. One of the studies reported a categorical outcome,[352] and the other two reported continuous outcomes of cognitive decline.[336,347] Given that there were only three eligible studies for this factor for Question 2, we include all studies in the current discussion. The three studies are summarized in Table 63; detailed evidence tables are provided in Appendix B. One study used a community sample in the United States,[336] one used a community sample in Singapore,[352]and the third study used a clinical sample in Europe.[347] The length of followup ranged from 1.5 to 6 years. Two studies used sample selection methods that minimized selection bias,[336,352] and the third study partially used such methods.[347] Both used self-report of current involvement and/or frequency of involvement in specific activities, a method of measuring exposure that has not been validated. Only one of the studies reported comparisons of baseline characteristics between those exposed and unexposed.[352] The cognitive outcomes for the study are described in Table 63. The analyses appear generally appropriate and controlled for relevant potential confounders, but the studies did not report a priori sample size calculations.

One study[347] reported that involvement in social activities was associated with less decline on the immediate and delayed recall trials of a verbal memory task ($0.01 < p < 0.05$). It is noteworthy that no adjustment was made for multiple statistical comparisons, and the three other cognitive measures did not show significant differences in rate of cognitive decline based on participation in social activities. Another study[336] found that higher levels of involvement in social activities were associated with slightly less decline on a global cognitive measure. The third study examined a wide range of leisure activities and found that individuals in the medium and high tertile levels of leisure activity were less likely to exhibit decline on the MMSE.[352] In addition, individuals who participated in at least one activity considered to be a "productive leisure activity" were less likely to decline on the MMSE, while those who participated in at least one social or physical leisure activity did not show such a benefit. Among APOE e4 carriers, those who participated in at least one physical leisure activity or one social leisure activity were significantly less likely to decline on the MMSE; this same association was not observed among APOE e4 non-carriers.

In conclusion, these studies provide preliminary evidence that a range of leisure activities may be associated with preservation of cognitive function. The findings are not entirely consistent, as two of the three studies reported an association between greater involvement in social activities and less cognitive decline, while one did not find such an association. In addition, the differences in how exposure was defined, the limited number of statistically significant associations among the multiple comparisons, and the relatively small effect sizes limit the conclusions that can be drawn. Further research is needed in this area.

Table 63. Leisure activities and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Bosma et al., 2002[347]	Clinical cohort – family practice clinics (830)	3 years	Self-report of activities described as "social activities" such as organizational memberships (e.g., clubs)	Longitudinal performance on the following cognitive measures: Stroop Color-Word Test , word list memory test, a letter-digit substitution test, semantic verbal fluency test, and the MMSE	Age Sex Educational level Baseline cognitive status Length of followup interval	At least 1 hour per week in social leisure activities was associated with less cognitive decline on the immediate recall trials of a word list memory task (β coefficient = 0.94; $p < 0.05$) and the delayed recall of the word list memory task (β = 0.30: $p < 0.05$)
Barnes et al., 2004[336]	Community cohort (6158)	6 years (mean)	Social activities scale (0 to 8 points) constructed from responses to following items: 1) Attending religious services 2) Going to a museum 3) Participation in activities or groups outside the home 4) A part-time or full-time job	Global composite index of scores on the MMSE, the immediate and delayed recall of the East Boston Story, and the oral version of the Symbol Digit Modalities Test	Age Race Sex Martial status Educational level Income	0.009 unit reduction of cognitive decline on the global composite index score for every point on the social engagement scale ($p < 0.001$).
Niti et al. 2008[352]	Community cohort (2611)	1.5 years (median)	Self-report of "social activities," including religious services, movies, going to restaurants or sports events, day or excursion trips, playing cards or other games, senior citizen club activities, and group recreational activities such as karaoke and dancing Self-report of "productive activities," including	Cognitive decline on the MMSE defined as a decrease of 1 or more points at followup assessments	Age Sex Educational level Baseline cognitive status APOE Functional status Number of co morbidities Vascular risk factor/events Depression	Compared to those who had low leisure activity levels the OR for cognitive decline among those with high levels of leisure activity was 0.62 (95% CI 0.46 to 0.84); among those who had medium leisure activity, the OR was 0.60 (0.45 to 0.79) Compared to those who did not engage in any productive activity, those who engaged in at least one productive activity had lower risk of cognitive decline: OR 0.36

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
			reading, music, media programs, computing, painting, gardening, preparing meals, shopping, unpaid and paid community work, and other leisure paid employment or business. Self-report of "physical activities," including walking, active sports or swimming, and tai chi		Smoking Alcohol	(95% CI 0.20 to 0.65) In the total sample, participation in at least one social or physical activity was not associated with cognitive decline. However, in the APOE carriers, those who participated in at least one physical activity (OR 0.34; 95% CI 0.17 to 0.68) or at least one social activity (OR 0.40; CI 0.16 to 0.99) were less likely to decline on the MMSE.

Abbreviations: APOE = apolipoprotein E gene; CI = confidence interval; MMSE = Mini-Mental State Examination; OR = odds ratio

Tobacco use. We identified one good quality systematic review, published in 2007, that examined the association between tobacco use and cognitive decline, cognitive impairment or cognitive performance change.[50] The review included three prospective cohort studies for cognitive performance change published between 1996 and 2004.[353-355] The three studies included a total of 7872 subjects; one was conducted in the United States, and the other two in European countries. The review also included three prospective cohort studies reporting a dichotomous measure of cognitive decline (776 subjects; two from the United States and 1 from Europe),[356-358] and three prospective cohort studies reporting cognitive impairment (8385 subjects; one each from the United States, Canada, and Australia).[74,359,360] Studies were selected that had at least two occasions of measurement, used cognitive measures compatible with those used by other studies, included at least a 12-month followup period, and measured exposure to smoking at baseline. The MMSE was the only cognitive measure common to enough studies to analyze cognitive performance change. Cognitive performance change was defined as a continuous measure of yearly change on the MMSE. The definitions for cognitive decline and cognitive impairment differed across studies, but in general terms cognitive decline was defined as a dichotomous variable based on cognitive measures that included more than just the MMSE. Cognitive impairment was a decline on cognitive measures sufficient to represent a pre-set definition of impairment. Study quality was not reported in this systematic review. Length of followup ranged from 2 to 7 years. The covariate adjustment for most studies included at least age and education; many studies included additional covariates such as sex, APOE, biological measures, and health conditions. The results with the most covariates were given preference when reporting the data from the individual studies. Exposure was determined by self-report, and smoking was classified as ever, current, former, or never smokers.

Studies were combined using fixed-effect meta-analyses if there was no evidence of heterogeneity. If heterogeneity was present, random-effects models were used. Standard χ^2 tests using a p-value of 10 percent were used to examine heterogeneity. The small number of studies within each group of studies with compatible measures precluded investigation of heterogeneity, using meta-regression, subgroup analyses, or assessment of publication bias. The results for the various exposure definitions and the outcomes measures are reported in Table 64. To briefly summarize the main findings, current smokers were more likely to show a greater decline on the MMSE than either former or never smokers. Current smokers were also more likely to be categorized as "cognitive decliners" compared to individuals who were former smokers and those who never smoked. Finally, former smokers showed greater yearly decline on the MMSE compared to those who never smoked.

Table 64. Smoking and risk of cognitive decline – results from studies reviewed by Anstey et al., 2007[50]

Comparison/Outcome assessed	Relative risk (95% CI)	Cognitive change*
Current smokers versus never smokers Yearly performance change on MMSE (n = 3 studies)	-	-0.13 (-0.18 to -0.08)
Ever smokers versus never smokers Cognitive impairment (decline on cognitive measure into preset impaired level) (n = 3 studies)	0.85 (0.35 to 2.09)	-
Former smokers versus never smokers Yearly performance change on MMSE (n = 3 studies)	-	-0.07 (-0.11 to -0.03)
Current smokers versus former smokers Yearly performance change on MMSE (n = 3 studies)	-	-0.07 (-0.13 to -0.02)
Current smokers versus former and never smokers Cognitive decline (dichotomous outcome, decliners versus non-decliners) (n = 3 studies)	1.41 (1.16 to 1.71)	-

*Linear regression coefficient (β) and 95% CI.
Abbreviations: CI = confidence interval; MMSE = Mini-Mental State Exam.

The authors noted that one limitation of the review was that the former smokers group includes a broad range of exposure periods. Unfortunately, there were not a sufficient number of studies with data on the number of smoking pack-years to use this as the exposure variable. Publication bias was not assessed formally. Quality ratings of the studies were not provided, but strict selection criteria may have increased the likelihood that only high quality studies were included in the review. The authors concluded that current smokers are at increased risk of cognitive decline compared to those who never smoked.

We identified five additional eligible cohort studies examining the association between smoking and cognitive decline.[257,258,266,271,361] These studies are summarized in the Table 65; detailed evidence tables are in Appendix B. Four of the five studies used a categorical outcome;[257,258,266,271] the fifth[361] assessed cognitive decline as a continuous variable. This latter study is included in the current discussion because it is the only one of the five studies that assessed the association of smoking and cognitive decline based on APOE e4 allele status. All five studies used samples drawn from the community; one also studied nursing home residents.[266] Three studies used U.S. samples,[258,271,361], one used an Australian sample,[257] and the other used a European sample.[266] In three of the studies, participants were cognitively normal at baseline.[257,266,361] In the other two studies, it is likely the vast majority of the participants were non-demented since one study[258] included only individuals with 3MS scores > 80 in an attempt to exclude individuals with cognitive impairment, and the other study had a 6-year period between the two cognitive assessments.[271] Length of followup ranged from 3.5 to 10 years (mean or median). All three studies used self-report history of smoking obtained at baseline to characterize exposure. The studies used sample selection methods to minimize selection bias; however, only three of the studies compared baseline characteristics to assess differences between exposed and unexposed.[258,271,361] The case definitions and cognitive outcomes used in the studies are described in Table 65. The analyses appear generally appropriate and controlled for relevant potential confounders, but none of the studies conducted a priori sample size calculations.

The results were inconsistent across studies, with two studies[258,271] reporting that those who did not smoke had greater likelihood of maintaining optimal cognitive function versus exhibiting minor cognitive decline. In one study, past smoking was associated with increased risk of MCI compared to never smoking,[257] but another study did not find a significant association between number of pack years of smoking and risk of incident MCI.[266] The fifth study[361] did not find a significant association between current smoking and cognitive decline on abstract reasoning-visuospatial tasks in either the group that was ≤ 75 years old or > 75 years old. However on memory tasks, current smokers over age 75 showed greater cognitive decline than individuals who did not currently smoke; there was no comparable difference among the group that was ≤ 75 years old. Three of the studies examined current smoking,[258,271,361] but only one of them[271] used the MMSE as the main cognitive measure, making it relatively comparable to the measures of exposure and outcome in the systematic review by Anstey et al.[50] In general terms, the findings from this study were consistent with those from the review, that is, current smoking was related to cognitive decline.

One study examined the association between current smoking and cognitive decline by APOE e4 allele status.[361] This study found that its reported association between current smoking and decline on memory tasks was limited to the group over age 75 years with no APOE e4 allele. This finding is generally consistent with those reported for current smoking and AD, that is, the statistically significant association found in the entire group was due to the association in the subgroup with no APOE e4 allele and not to the subgroup with at least one APOE e4 alleles.

In conclusion, these studies provide fairly consistent evidence for an association between current smoking and increased risk of cognitive decline. The evidence on past smoking is less consistent.

Table 65. Tobacco use and risk of cognitive decline – recent cohort studies

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Barnes et al., 2007[271]	Community cohort (9704)	6 to 15 years (median, 10)	Self-report smoking history	Cognitive decline on a 26-point version of MMSE Grouped as "maintain cognition," "minor decline," or "major decline"	Age Educational level Baseline cognitive status Study site	Risk of maintaining optimal cognitive function versus minor cognitive decline related to lack of smoking: OR 1.73 (95% CI 1.30 to 2.30)
Reitz et al., 2005[361]	Community cohort (791)	5-year interval	Self-report smoking history	Decline on cognitive tests	Age Educational level Race Sex HTN Heart disease DM APOE	Estimated beta coefficient (SE): <u>Abstract/visuospatial</u> ≤ 75 years: No significant interaction between time x current smoking (beta = 0.1[0.5]; p = 0.9) > 75 years: No significant interaction between time x current smoking (beta = -0.4 [0.5]; p = 0.5) <u>Memory</u> ≤ 75 years: No significant difference between time x current smoking (beta = -1.1 [1.6]; p = 0.5) > 75 years: Significant interaction between time x current smoking (beta = -4.0 [1.8]; p = 0.02) <u>APOE -/-</u> *Memory* ≤ 75 years: Time x current smoking (beta = -1.3 [1.9]; p = 0.5) > 75 years: Time x current smoking (beta = -5.5 [2.3]; p = 0.016) *Abstract/visuospatial* ≤ 75 years: Time x current smoking (beta =0.4 [0.6]; p = 0.5) > 75 years: Time x current smoking (beta= -0.3 [0.7]; p = 0.7)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
						<u>Among individuals with one or more APOE e4 alleles</u> *Memory* ≤ 75 years: Time x current smoking (beta =-0.1 [2.7]; p = 0.9) > 75 years: Time x current smoking (beta = -0.9 [2.8]; p = 0.7) *Abstract/visuospatial* ≤ 75 years: Time x current smoking (beta = -0.6 [1.0]; p = 0.5) > 75 years: Time x current smoking (beta = -0.4 [1.2]; p = 0.7)
Solfrizzi et al., 2004[266]	Community cohort, including institutiona-lized subjects (1566)	3.5 years	Self-report smoking history	Variation of Petersen MCI criteria	Age Educational level Total cholesterol HTN Coronary artery disease	RR Pack years: 0.94 (95% CI 0.62 to 1.42)
Yaffe et al., 2009[258]	Community cohort (2509)	8 years	Self-reported information on current smoking	Longitudinal performance on the 3MS. Maintainers: Predicted slopes of 0 or greater (indicating no change or improvement in cognitive scores over time) Minor decliners: Predicted slopes less than 0 decline in cognitive score over time) but no more than one SD below the	Age Race Educational level APOE genotype	When controlling for about 20 other factors associated with being a maintainer or decliner, risk of being a cognitive maintainer vs. a minor decliner for individuals who did not currently smoke vs. current smokers: OR 1.84 (95% CI 1.14 to 2.97) Risk of being a major decliner vs. a minor decliner: OR 1.15 (95% CI 0.72 to 1.84)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
				mean of the slopes Major decliners: Predicted slopes more than 1 SD below the mean		
Cherbuin et al., 2009[257]	Community cohort (2082)	4 years	Self-report information about current and past smoking	Published criteria for MCI, AAMI, AACD and other cognitive disorder	Age Sex Educational level	Incident MCI: Past smoking was associated with higher risk of MCI compared to never smoking (OR 3.22; 95% CI 1.05 to 9.87, p = 0.04) Incident any MCD: Past smoking was associated with higher risk of MCD compared to never smoking (OR 1.97; 95% CI 1.12 to 3.44, p = 0.03)

Abbreviations: 3MS = Modified Mini-Mental State Examination; AACD = aging-associated cognitive decline; AAMI = age-associated memory impairment; APOE = apolipoprotein E gene; APOE e4 = e 4 allele of the apolipoprotein E gene; CI = confidence interval; HTN = hypertension; DM = diabetes mellitus; MCD = mild cognitive disorder; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NS = not statistically significant; OR = odds ratio; RR = relative risk; SD = standard deviation; SE = standard error

Alcohol use. We identified a single, good quality systematic review, published in 2009, that examined the association between alcohol use and cognitive decline.[51] The review included two prospective cohort studies for cognitive decline published in 2000 and 2005.[220,362] The two studies were community samples and included a total of 2192 subjects; one was conducted in the United States, and the other in a European country. Studies were selected that had measured cognition at both baseline and followup periods and either implemented a dementia assessment at baseline, which excluded those participants with cognitive impairment or dementia, or adjusted for incident dementia and/or baseline cognition performance in analyses. Included studies also had at least a 12-month followup period, had cognitive decline as an outcome, and measured exposure to alcohol at baseline or during the followup period prior to the final followup examination. Study participants were non-demented at baseline. The meta-analysis was based on current alcohol use, but one of the studies[220] also collected data on former alcohol users versus lifetime abstainers.

The cognitive outcome was defined as longitudinal change on the MMSE for one study.[362] and change on a composite score of multiple cognitive measures for the other study.[220] There was not a structured quality assessment of the studies reported in this systematic review; however the strict inclusion/exclusion criteria provided an indirect assessment of quality, and the study characteristics for key design variables were reported. Length of followup ranged from 4 years in one study[362] to an average of 7.3 years in the other study.[220] No information was provided on the followup rates in the studies. The covariate adjustment for the two studies included at least age, sex, education, baseline cognitive score, and depressive symptoms; each study had additional covariates such as health behaviors and conditions. The results with the most covariates were given preference when reporting the data from the individual studies. Exposure was determined by self-report and alcohol use was classified as drinkers versus nondrinkers.

Studies were combined using fixed-effect meta-analyses if there was no evidence of heterogeneity. If heterogeneity was present, random-effects models were used. Standard χ^2 tests using a P value of 10 percent were used to examine heterogeneity. Publication bias was not formally assessed.

The results for cognitive decline in drinkers versus non-drinkers are reported in Table 66. The test for heterogeneity was significant ($\chi^2_{[1]} = 11.80$, P = 0.00006), suggesting that the pooled results from only two studies may not be reliable. To summarize the main findings, the direction of the relative risk suggested that drinkers may have a lower risk of cognitive decline, but the result did not approach standard statistical significance levels.

Table 66. Alcohol use and risk of cognitive decline – results from studies reviewed by Anstey et al., 2009[51]

Comparison/Outcome assessed	Relative risk (95% CI)
Drinkers versus nondrinkers (n = 2 studies)	0.28 (0.03 to 2.83)

Abbreviation: CI = confidence interval

As discussed above under Question 1, the authors of the systematic review noted a number of complicating factors in the study of alcohol use as a risk factor for late-life cognitive outcomes. These factors make interpretation of the meaning of both significant and null results challenging. Publication bias was not assessed formally in this systematic review, but the authors suggested that the potential for such bias was likely reduced because of the inclusion of studies from article

reference lists and articles that did not focus on alcohol use, but in which alcohol use was a covariate. Quality ratings of the studies were not provided, but strict selection criteria may have increased the likelihood that only high-quality studies were included in the review. The authors concluded that the pooled analysis showed no significant association between alcohol use and cognitive decline, but the measure of heterogeneity indicated that the results from the two studies combined may not be reliable.

We identified five additional eligible cohort studies examining the association between alcohol use and cognitive decline published since June 2006.[257,258,363-365] These studies are summarized in Table 67; detailed evidence tables are in Appendix B. In two of the studies[257,365] participants were cognitively normal at baseline, and in two other studies the vast majority of participants are assumed here to have been non-demented based on either minimum cognitive scores required for inclusion in the study[364] or mean age and mean cognitive score for the group.[363] The fifth study[258] included individuals who scored 80 or higher on the 3MS; thus it may have included some individuals with cognitive impairment and dementia. Two of these studies used the categorical outcome of incident mild cognitive impairment (MCI),[257,365] and one used a categorical outcome indicating maintenance of cognition or minor or major decline. The other two studies[363,364] assessed cognitive decline as a continuous variable. All five studies used samples drawn from the community; one of them also studied nursing home residents.[365] Two studies used a U.S. sample,[258,363] two used European samples,[364,365] and one used an Australian sample.[257] The average length of followup ranged from 2.2 to 8 years. The studies used self-report history of current alcohol use obtained at baseline to characterize exposure during late life. Four of the studies used sample selection methods to minimize selection bias; [257,258,363,365] the inclusion criteria for the fifth study[364] required that participants have vascular risk factors or vascular disease, which may have confounded the association between alcohol and cognitive change. Three studies compared baseline characteristics to assess differences between exposed and unexposed.[258,363,364] The case definitions and cognitive outcomes for the studies are described in Table 67. The analyses appear generally appropriate and controlled for relevant potential confounders, but none of the studies conducted a priori sample size calculations.

The results on incident MCI were inconsistent between the two studies evaluating this outcome, with one reporting no association between use of alcohol and risk of incident MCI,[365] and the other showing that drinkers overall had a lower risk of incident MCI compared to non-drinkers.[257] This latter study also showed a U-shaped quadratic relationship with very low and very high alcohol intake being associated with higher risk of MCI compared to moderate alcohol intake. The third study using a categorical outcome for cognitive decline found no significant association between alcohol intake and cognition, but the odds ratios were in the direction of more than one drink per day being protective for cognition.[258] This study simultaneously examined the association between about 20 factors and cognitive decline; alcohol was not the focus of the study. The two studies assessing rate of cognitive decline as a continuous measure were consistent regarding the use of any alcohol providing greater preservation of cognition over time. One study[364] reported a significant association (but negligible effect size) between alcohol use and maintenance of performance on the MMSE. However, this study did not find an association between alcohol intake and longitudinal performance on measures assessing other areas of cognition, such as memory and executive function, which are domains that typically show decline in the early stages of AD. The other study[363] showed a dose-response effect in which greater amounts of alcohol per week were associated with less decline on the modified Telephone Interview for Cognitive Status (TICS), a measure of cognitive status similar to the

MMSE. This dose-response association was not modified by the presence of an APOE e4 allele. Interestingly, this study did not find that an excessive amount of alcohol (i.e., more than two drinks per day) had a detrimental effect on cognition.

In conclusion, the results are inconsistent regarding the association between cognitive decline and alcohol use in any amount. Obvious differences between the studies do not point to a clear explanation for these inconsistencies.

Table 67. Alcohol and risk of cognitive decline – recent cohort studies

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Wright et al., 2006[363]	Community cohort (1428)	0.5 to 4.4 years (mean, 2.2)	Self-report alcohol history	Cognitive decline on a 51-point version of the TICS-m	Age Race Sex Educational level Baseline cognitive status Interval between cognitive testing Health insurance status HDL-C level BMI HTN DM Cardiac disease	Drinking less than one drink a week (P = 0.09), between one drink weekly and up to two drinks daily (P = 0.001), and more than two drinks daily (P = 0.003) were associated with less cognitive decline on the TICS-m compared to never drinkers
Stott et al., 2008[364]	Community cohort (5804)	3.2 years (mean)	Self-report alcohol history	Decline on cognitive tests	Age Country Educational level Baseline cognitive status Smoking status BMI Weight Incident stroke History of vascular disease Test version	Rate of cognitive decline was similar for drinkers and non-drinkers for all cognitive domains, except the MMSE, which declined significantly less in female drinkers compared to non-drinkers (attenuated rate of decline = 0.05 MMSE units per annum, P = 0.001)
Solfrizzi et al., 2007[365]	Community cohort, including institutiona-lized subjects (1566)	3.5 years	Self-report alcohol history	Variation of Petersen MCI criteria	Age Sex Educational level Smoking CAD Diabetes Hypertension	No significant associations between any levels of drinking and the incidence of MCI in non-cognitively impaired individuals vs. abstainers

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
					Stroke Cholesterol	
Cherbuin et al., 2009[257]	Community cohort (2082)	4 years	Self-report alcohol history	Published criteria for MCI, AAMI, AACD, and other cognitive disorder	Age Sex Educational level	Incident MCI: Alcohol intake associated with lower risk of MCI compared to abstainers (OR 0.59; 95% CI 0.37 to 0.92; p = 0.021) Quadratic model: U-shaped association showing higher risk for low and high drinking groups (OR 1.58; 95% CI 1.18 to 2.11; p = 0.002) Incident any mild cognitive disorder (MCD): Alcohol intake associated with lower risk compared to abstainers (OR 0.75; 95% CI 0.57 to 1.00; p = 0.046) Quadratic model: U-shaped association showing non-significant trend toward higher risk for low and high drinking groups (OR 1.17; 95% CI 0.98 to 1.40; p = 0.087)
Yaffe et al., 2009[258]	Community cohort (2509)	8 years	Self-report alcohol history	Change on the 3MS Maintainers- 0 or greater predicted slope over time based on linear mixed model analyses Minor decline - predicted slope less than 0, but no more than one SD below the mean of the slopes Major decline -	Age Race Educational level APOE genotype Reading ability Volunteer work Caregiver status Social support Living situation Self-rated health Physical exercise Smoking Depression BMI Hypertension	Maintainers vs. minor decliners (reference): > 1 drink alcohol daily: OR 1.33 (95% CI 0.91 to 1.93) Major declines vs. minor decliners (reference): > 1 drink alcohol daily: OR 0.67 (95% CI 0.36 to 127)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
				predicted slope more than 1 SD below the mean	Diabetes Stroke C-reactive protein IL-6 Triglycerides Fasting glucose	

Abbreviations: 3MS = Modified Mini-Mental State Examination; AACD = aging-associated cognitive decline; AAMI = age-associated memory impairment; APOE = apolipoprotein E gene; BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; DM = diabetes mellitus; HDL-C = high density lipoprotein cholesterol; HTN = hypertension; IL-6 = interleukin-6; MCD = mild cognitive disorder; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; OR = odds ratio; SD = standard deviation; TICS-m = Telephone Interview for Cognitive Status (modified version)

Toxic Environmental Exposures

We identified no systematic reviews or primary studies that examined toxic environmental exposures and the risk of cognitive decline.

Genetic Factors

Although there is an extensive literature examining genetic factors associated with AD, the literature linking genes and cognitive decline is more limited. The relation between genetic polymorphisms and cognitive change has been studied for the apolipoprotein E gene (APOE). APOE has three common alleles (e2, e3, and e4) that act as susceptibility factors for late-onset (age ≥ 65 years) AD. APOE e4 increases the risk of AD in a dose-dependent fashion, and e2 reduces the risk.

We identified 15 cohort studies involving 8509 subjects that examined the association between APOE and the risk of cognitive decline.[183,258,260,262,267,274,284,330,331,366-371] These studies are summarized in Table 68; detailed evidence tables are in Appendix B. Four of the studies reported a categorical outcome,[183,258,267,367] and the other 11 reported continuous outcomes.[260,262,274,284,330,331,366,368-371] Fourteen were community samples, and one sample came from a clinical trial.[284] One sample was from Australia,[331] four from Europe,[267,284,369,371] and 10 from the United States.[183,258,260,262,274,330,366-368,370] The length of followup ranged from 1 to 14 years, and approximately 60 percent of subjects were women. All of the studies used sample selection methods to minimize selection bias and reported comparisons of baseline characteristics between those exposed and unexposed. The case definitions and cognitive outcomes for the studies are described in Table 68. None of the studies reported a priori sample size calculations. The analyses appear generally appropriate, with all of the studies using education as a covariate, and all but one adjusting for age and sex. The one study that did not adjust for age or sex had a sample with a narrow age range (ages 65 to 69).[331] The studies used different baseline cognitive criteria for inclusion and some may have included individuals with mild cognitive impairment. One study included some individuals with dementia at baseline,[331] but we report here only the analyses that excluded those individuals. The followup rates for four of the studies were fairly high, but one study had a followup rate of about 50 percent when combining non-participation due to both attrition and exclusion criteria.[368]

Generally, various studies reported that APOE e4 was associated with greater decline on some, but not all, cognitive measures. Five studies reported a categorical outcome, and all found that APOE e4 allele increased the risk of cognitive decline.[183,258,267,330,367] Tervo et al.[267] reported that subjects with an APOE e4 were more likely to receive a diagnosis of MCI than those without an APOEe4 (OR 2.23; 95 percent CI 1.23 to 4.05). Bretsky et al.[367] assessed global cognitive function using the SPMSQ and found that subjects with an APOEe4 allele were at increased risk for decline (OR 2.3; 95 percent CI 1.5 to 3.4). Yaffe et al.[258] divided subjects into cognitive maintainers, minor decliners, and major decliners based on their performance on the modified MMS test (3MS). Investigators reported that major decliners were more likely to inherit an APOE e4 than minor decliners (OR 2.31; 95 percent CI 1.75 to 3.05). Presence of an APOEe4 allele was not, however, significantly different in those who maintained cognitive performance compared to those with minor declines. Shadlen et al.[330] used the cognitive abilities screening instrument (CASI) to assess performance at baseline and after 6 years. At followup 6 percent of the 2168 subjects had a decline of ≥ 1.5 SD on the CASI. Individuals who were

homozygous for APOE e4 were at increased risk for decline compared to non-e4 subjects, but e4 heterozygotes were not. Tyas et al.[183] reported on data from 470 subjects in the Religious Orders Study followed for 1 to 12 years and found that subjects with an APOE e4 allele had an increased risk of transition from normal cognition to mild cognitive impairment compared to subjects without an APOE e4 allele (OR 1.87; 95 percent CI 1.27 to 2.73).

Several studies used a battery of tests to assess longitudinal cognitive function. Comparison across studies is difficult because of the wide variety of non-overlapping tests used. Blair et al.[368] studied subjects from the Atherosclerosis Risk in Communities (ARIC) project over a 6-year period. Investigators found a racial difference in APOE genotype effect. In Caucasians, decline on the Digit Symbol Substitution Test (DSST) and the Delayed Word Recall (DWR) test was correlated with APOE genotype, with the e2 group showing less decline than the e3 group, which in turn showed less decline than the e4 group. Among African-Americans, an APOE correlation similar to that observed in Caucasians was shown for DSST, but not DWR. Word fluency was not correlated with APOE genotype in either group. Knopman et al.[260] extended the findings with the ARIC population reported by Blair et al.[368] After 14 years of followup, APOE e4 genotype was still associated with a more rapid decline in DSST and DWR, but not WF, but the differential race effect was no longer significant.[260] Christensen and colleagues performed the MMSE, symbol digit modality, reaction time, California Verbal Learning test, and digits backward, and found that APOE e4 was associated with greater decline on the MMSE, but not any of the other cognitive measures.[331] Interpretation of the results for these multivariate analyses is problematic because of the large number of analyses performed without correction for multiple comparisons. Haan et al.[274] reported that APOE e4 was associated with a higher annual rate of decline on the DSST, but not on the 3MS. Staehelin et al.[369] examined free recall, reaction time, and the WAIS-R vocabulary test and found that baseline scores were lowest in subjects who were hetero- or homozygous for APOEe4, but after 2 years there was no APOE genotype-related change in performance on any measure. Yaffe et al.[370] followed a cohort of Caucasian women recruited for an osteoporotic fracture study and found that after an average followup of 6.4 years, women with an APOE e4 allele had a greater decline on all tests (modified MMSE, 26 points, P = 0.01; DSST, P = 0.05; Trails B, P = .0 503). A similar association between decline on DSST in individuals and APOE e4 was also reported by Blair and Knopman.[260,368] Packard and colleagues[284] analyzed the association between APOE genotype and cognitive decline in 5804 subjects from the PROSPER trial of pravastatin in hypercholesterolemia. Subjects were between the age of 70 and 82 and were followed for an average of 3.2 years. Investigators reported that subjects with an APOE e4 allele had poorer baseline performance on immediate and delayed memory scores, and slower information processing. Subjects with APOE e4 also showed a greater decline in immediate and delayed recall, but not significant change in speed of information processing, as measured by the Stroop test.[284]

Three studies reported an interaction effect for APOE e4 and diabetes or hypercholesterolemia, such that the presence of at least one e4 allele was associated with greater decline among individuals with any of these medical conditions.[262,274,368] However, one of these studies reported that this interaction was evident only on the 3MS,[274] and another reported it for the DSST.[368] Carmelli and colleagues found a significant difference in MMSE, DSST, and BVRT.[262] Shadlen et al. reported that lower education was associated with steeper 4-year declines on CASI in APOE e4 homozygotes, but not in heterozygotes, suggesting that modifiable factors, such as education, could mitigate the association of this genetic risk factor on cognitive

decline.[330] Dik et al. examined the association between APOE genotype in cognitively normal subjects (MMSE > 26) and subjects with mild cognitive impairment (MMSE 21 to 26).[371] Investigators reported that APOE e4 is a risk factor for memory decline, but only in cognitively impaired individuals (MMSE 21 to 26). No association between decline and APOE e4 was found in subjects with baseline MMSE > 26.

Two studies also found that the APOE e2 allele may provide some protection against cognitive decline compared to both APOE e3 and e4.[366,368] Wilson and colleagues reported that inheriting an APOE e2 allele was associated with a reduced rate of decline in episodic memory, while inheriting an APOEe4 allele was associated with an increased rate of decline in semantic memory, episodic memory, and perceptual speed.[366] Blair et al. found that APOE e2 was associated with a slower rate of decline in DSST and DWR, but not WF, compared to non-APOE e2 genotypes in Caucasians, but not in DWR for African-Americans.[368]

In summary, the majority of studies suggest that APOE e4 is associated with an increased rate of cognitive decline in elderly individuals, especially on some memory tasks (DWR) and tasks of perceptual speed (e.g., the DSST). Not all cognitive domains appear to be affected by APOE genotype, and there is variability between studies. There is some evidence that APOE e2 protects against memory decline, which is consistent with its proposed protective role against AD, but more data are needed. The effect of APOE on cognitive decline in African-Americans remains uncertain and will require studies with larger numbers of participants. There is modest evidence about interactions between APOE genotype and other risk factors, such as diabetes, hypercholesterolemia and education, but no firm conclusions can be drawn. Data examining the role of other genetic factors linked to AD, such as PICALM and CLU in the rate of cognitive decline are lacking.

Table 68. APOE genotype and risk of cognitive decline

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Wilson et al., 2002[366]	Community cohort (669)	2 to 8 years	APOE genotype	Change on index of combined cognitive tests in separate cognitive domains Tests listed in table legends	Age Sex Education	e2 semantic memory decline slower than e3/3 e4 decline > e3 in semantic memory and perceptual speed, not working memory or visuospatial ability
Bretsky et al., 2003[367]	Community cohort (965)	7 years	APOE genotype	Decline of ≥ 1 SD on individual tests and summary scores as listed in table legend	Age Sex Race Education	Risk of decline of e4 carriers on global cognitive score: OR 2.0 (95% CI 1.1 to 3.6)
Blair et al., 2005[368]	Community cohort (1693 African-Americans and 6202 Caucasians used in analysis)	6 years	APOE genotype	Decline on DWR, DSST, and COWA, categorized by quintiles	Age Sex Education Baseline cognition Cigarette smoking NSAIDs DM HTN Hypercholesterolemia	Comparing quintile of greatest change to all other quintiles, risk for decline in AA, e4/4 compared to e3/3: DWR OR 1.72 (95% CI 0.97 to 3.06) DSST OR 1.86 (1.06 to 3.27) Risk for decline in Caucasians. Compared to e3/3 genotype e2 group DWR OR 0.78 (95% CI 0.61 to 0.98); e4 group (e3/4 or e2/4) DWR OR 1.19 (1.01 to 1.41) e4/4 DWR OR1.53 (0.95 to2.45) DSST: e4/4 compared to e3/3: OR 2.02 (1.31 to 3.12)
Christen-sen et al., 2008[331]	Community cohort (2021)	4 years	APOE genotype	Decline on: MMSE SDMT Reaction time CVLT Digits backwards	Educational level Premorbid intelligence History of stroke Current HTN	APOE e4 associated with greater decline on MMSE only (F = 3.55; p = 0.029), but no difference on other tests.

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Haan et al., 1999[274]	Community cohort (3622)	7 years	APOE genotype HTN DM	Annual rate of change on 3MS and DSST	Age Race Sex Education Incident stroke	Higher annual rate of decline on DSST in APOE e4 positive versus e4 negative individuals ($p < 0.0001$). No difference on 3MS Interaction between APOE e4 and diabetes ($p < 0.001$) on 3MS: APOE e4+ and diabetes+: -0.39 APOE e4+ and diabetes-: -0.70 APOE e4- and diabetes+: -0.46 APOE e4- and diabetes-: -0.23
Knopman et al., 2009[260]	Community cohort (1130)	Median 14 years	APOE genotype	DSST DWR WF	Age Race Sex Educational level Vascular factors Time Risk factor x time interaction	Difference in average baseline cognitive test scores (P value) – APOE genotype: DSST: 1.06 (0.03) DWR: 0.17 (0.49) WF: 0.59 (0.405) Difference in annual rate of change (P value) – APOE e4 genotype: DSST: -0.10 (0.004) DWR: -0.03 (< 0.001) WF: -0.04 (NS)
Tervo et al., 2004[267]	Community cohort (747)	3.26 ± 0.7 years	APOE genotype	Clinical Dementia Rating (CDR): MCI diagnosed if score of 0.5 and if subject scored 1.5 SD below average on at least one memory test	Age Race Sex Educational level Baseline cognitive status	66 subjects (8.8%) had converted to MCI. The global incidence rate of MCI was 25.94/1,000 person-years. Persons with higher age (OR 1.08, 95% CI 1.01 to 1.16), APOE e4 allele carriers (OR 2.04, 95% CI 1.15 to 3.64) and persons with medicated hypertension (OR 1.86, 95% CI 1.05 to 3.29) were more likely to convert to MCI than those individuals of lower age and without an APOE e4 allele or medicated hypertension.

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
Staehelin et al., 1999[369]	Community cohort (332)	2 years	APOE genotype	Computerized test for free recall and information processing speed Reaction time WAIS-R vocabulary subtest – define 32 words	Age Sex Educational level Lipids Smoking	At baseline: Adjusting for age and education: e4/4 and e3/4 performed lowest in free recall, reaction time, and WAIS-R vocabulary subtest compared to e3/3 or carriers of one or two e2 alleles (free recall P = 0.05; reaction time P = 0.009; WAIS-R vocabulary subtest P < 0.05) No significant changes in any outcome measure (free recall, reaction time, or WAIS-R vocabulary subtest) after 2 years in any APOE genotype
Shadlen et al., 2005[330]	Community cohort (HMO members) (2140)	3.29 years	APOE genotype	Change in CASI score	Age Race Sex Years of followup Depression Diabetes Hypertension Cerebrovascular disease	GEE analysis: Risk factors associated with change in global cognitive performance No e4 – reference One e4 allele: coefficient = -0.23 (95% CI -2.5 to 2.05; P = 0.846) Two e4 alleles: coefficient = -10.08 (95% CI-16.24 to -3.92; P = 0.001)
Yaffe et al., 1997[370]	Clinical cohort - subjects in the multi-center Study of Osteoporotic Fractures (1248)	6 years	APOE genotype	Modified MMSE (max score 26) Trails B DSST Cognitive decline was defined on each or any test if a woman had the largest 10th percentile reduction in performance from initial score to repeat testing	Age Educational level Baseline cognitive status Depression Presence of severe tremor	Presence of an APOE e4 was significantly associated with worsening on all cognitive tests at followup compared to no e4 group (modified MMSE P = 0.01; DSST P = 0.05; Trails B P = 0.003) Incidence of cognitive decline was 1.6 times higher in the e4 group (P < 0.03) and ranged from 1.2 times higher for Trails B to 2.4 times higher for modified MMSE. Homozygotes declined almost twice as fast as heterozygotes on all tests except Trails B.

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
						Reduction on the modified MMSE was 0% for no e4; 1.9% for 1 e4; and 3.7% for 2 e4s (P < 0.001) Reduction on DSST was 6.2% for no e4; 9% for 1 e4 and 17.5% for 2 e4s (P = 0.04) Reduction on Trails B was 5.9% for no e4; 25% for 1 e4 and 10.9% on 2 e4s (P = 0.002)
Yaffe et al., 2009[258]	Community cohort (2509)	8 years	APOE genotype	Slopes of 3MS scores were estimated by best linear unbiased predictions using a linear mixed model with random intercepts and slopes. Slopes of 0 or greater were classified as maintainers. Those with predicted slopes less than 0, but not more than one SD below the mean of the slopes were classified as minor decliners. Those with predicted slopes more than 1 SD below the mean were classified as major decliners.	Age Race Educational level APOE genotype	Minor vs. major decliners: APOE e4: OR 2.31 (95% CI 1.75 to3.05) APOE e4 was not associated with being a maintainer vs. a minor decliner: OR 0.8 (95% CI 0.62 to 1.02)
Carmelli et al., 1998[262]	Community cohort (NHLBI WWII twin substudy) (410)	10 to 25 years	Mid-life hyperglycemia (1-hour postprandial glucose > 200 or use of hypoglycemic agent or insulin) APOE genotype	Change in test scores: MMSE, DSST, BVRT	Age Race Sex Baseline scores Incident cardiovascular disease	Mean change (SD) APOEe4+ and hyperglycemia+: MMSE: 1.66 (0.39) DSST: 7.84 (1.08) BVRT: 1.05 (0.26) APOEe4+ and hyperglycemia-: MMSE: 0.73 (0.28) DSST: 4.47 (0.76)

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
						BVRT: 0.53 (0.19) APOEe4- and hyperglycemia+: MMSE: 0.47 (0.2) DSST: 4.14 (0.56) BVRT: 0.84 (0.14) APOEe4- and hyperglycemia-: MMSE: 0.47 (0.16) DSST: 3.34 (0.45) BVRT: 0.37 (0.11) All scores are significantly different from 0 and statistically significant at $p < 0.05$
Dik et al., 2000[371]	Community cohort (1243)	3.1 years	APOE genotype	MMSE; AVLT (3 trials); memory decline was defined as ≥1 SD mean change score on immediate recall, delayed recall, and retention based on AVLT	Age Sex Educational level APOE e4 carriers APOE e4 non-carriers MMSE 27-30 (normal cognition) MMSE 21-26 (impaired cognition)	In subjects with MMSE 21-26 and APOE e4 (adjusted for age, sex, education and baseline recall scores): Decline on immediate recall: OR 3.8 (95% CI 1.4 to 10) Decline on delayed recall: OR 2.9 (1.2 to 7.0) Decline on retention: OR 3.3 (1.1 to 10.1) No association of decline in cognitively normal subjects with APOE e4
Packard et al., 2007[284]	Clinical cohort (PROSPER trial) (5804)	3.2 years	APOE genotype	MMSE, picture-word learning test, Stroop color word test, letter digit coding test	Age Sex Country Education History of vascular disease MI Stroke	At baseline, subjects with APOE e4versus those without e4 had poorer memory performance (mean score difference -0.20 [95% CI -0.31 to -0.09] for immediate recall and -0.32 [-0.48 to -0.16] for delayed recall) and slower information processing (difference in Stroop, 2.79 seconds [95% CI 1.20 to 4.28]; Letter-Digit score, -0.36 [-0.77 to 0.05]). Subjects with APOE e4 showed

Study	Sample (n)	Followup	Exposure	Case definition	Confounding adjustment	Results
					TIA Smoking Antihypertensive medication BP BMI DM Triglyceride Treatment allocation APOE e4 Baseline cognitive test scores	a greater decline in immediate (-0.22, 95% CI -0.33 to -0.11) and delayed (-0.30, -0.46 to -0.15) memory scores but no significant change in speed of information processing (Stroop P = 0.17; Letter-Digit P = 0.06). Memory scores decreased 2.5% from baseline in those without e4, 4.3% in e4 heterozygotes (P = 0.01 for immediate and P = 0.03 for delayed, vs. no e4), and 8.9% to 13.8% in e4 homozygotes (P = 0.04 for immediate and P= 0.004 for delayed, vs. heterozygotes). APOE e4 was associated with greater decline in instrumental activities of daily living (P < 0.001).
Tyas et al., 2007[183]	Community cohort (470) Religious Orders Study	1-11 years	APOE genotype	Subjects performed four CERAD tests, MMSE and an ADL screen. Subjects with mild cognitive impairments had at least one specific area of impaired cognitive function, such as memory or naming, but had intact global cognitive ability and ADL.	Age Education APOE Prior cognitive state	Transition from intact to MCI – APOEe4 present: OR 1.87 (95% CI 1.27 to 2.73) Transition from intact to global impairment – APOEe4 present: OR 3.02 (1.87 to 4.89)

Abbreviations: 3MS = Modified Mini-Mental State Examination; ADL = activities of daily living; APOE = apolipoprotein E gene; APOE e2/e3/e4 = epsilon 2/3/4 allele of the apolipoprotein E gene; AVLT = Auditory Verbal Learning Test; BVRT = Benton Visual Retention Test; CASI = Cognitive Abilities Screening Instrument; CDR = Clinical Dementia Rating; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; COWA = Controlled Oral Word Association test; CVLT = California Verbal Learning Test; DM = diabetes mellitus; DSST = Digit Symbol Substitution Test; DWR = Delayed Word Recall; GEE = Generalized estimated equations; HTN = hypertension; MCI = mild cognitive impairment; MI = myocardial infarction; MMSE = Mini-Mental State Examination; NS = not statistically significant; NSAIDs = non-steroidal anti-inflammatory drugs; OR = odds ratio; SD = standard deviation; SDMT = Symbol Digit Modalities Test; TIA = transient ischemic attack; Trails B = Trail Making Test Part B; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WF = Word Fluency Test

Key Question 3 – Interventions to Delay the Onset of Alzheimer's Disease

Key Question 3 is: What are the therapeutic and adverse effects of interventions to delay the onset of Alzheimer's disease? Are there differences in outcomes among identifiable subgroups?

Nutritional and Dietary Factors

B vitamins and folate. There were no studies identified that used B vitamins or folate in RCTs to examine prevention of AD.

Other vitamins. We identified one RCT that examined the effect of supplemental vitamin E on progression of amnestic MCI to AD.[372] Participants were recruited from 69 Alzheimer's Disease Cooperative Study (ADCS) sites throughout the United States and Canada. Inclusion criteria were: a diagnosis of amnestic MCI; impaired memory; a Logical Memory delayed-recall score approximately 1.5 to 2 SD below an education-adjusted norm; a Clinical Dementia Rating Scale Score (CDR) of 0.5; a score of 24 to 30 on MMSE; and age between 55 to 90 years. There were three treatment arms: (1) 2000 IU of vitamin E, placebo donepezil, and multivitamin daily; (2) 10 mg of donepezil, placebo vitamin E, and a multivitamin daily; and (3) placebo vitamin E, placebo donepezil, and a multivitamin daily (placebo group). The trial lasted for 3 years, during which participants were assessed every 6 months. A total of 769 participants were randomized, of which 230 discontinued due to death, adverse events, or withdrawal of consent. Followup rates did not differ by treatment or placebo groups. The primary outcome was incident AD determined by standard assessment procedures and diagnostic criteria. Compared to the placebo group, the group treated with vitamin E did not show a difference in their rate of progression from amnestic MCI to AD (HR 1.02; 95 percent CI 0.74 to 1.41; P = 0.91).

Gingko biloba. We identified one RCT that examined the effectiveness of gingko biloba versus placebo in reducing the incidence of AD in older individuals with normal cognition and those with mild cognitive impairment.[373] Volunteers aged 75 years or older were recruited using voter registration and other purchased mailing lists from four U.S. communities with academic medical centers. To enroll in the study, individuals needed to have a proxy informant who was willing to be interviewed every 6 months. Individuals with prevalent dementia were excluded. There were additional exclusion criteria primarily related to medication use that are outlined the in evidence table in Appendix B. The treatment group took two daily doses of 120 mg gingko biloba extract; the placebo group took placebo pills on the same schedule. At the end of the trial, 60 percent of the active participants were taking their assigned study medication, and compliance did not differ between the two groups. A total of 3069 individuals were enrolled and randomized, of which 482 had a diagnosis of MCI at enrollment and the remainder were considered cognitively normal. Primary outcomes were known on 93 percent of the participants at the end of the study. The primary outcome was a diagnosis of dementia. Secondary outcomes were to evaluate the effect of gingko biloba on the following end points: overall cognitive decline, functional disability, total mortality, and incidence of cardiovascular disease. Only results on the primary outcome were presented in this article. The trial results showed that the HR for the entire sample for AD for the treatment versus the placebo groups was 1.16 (95 percent CI 0.97 to 1.39; P = 0.11); the HR > 1.0 suggests increased risk of AD for gingko biloba users. Gingko biloba also had no effect on the rate of progression to AD in participants with MCI (HR 1.10; 95

percent CI 0.83 to 1.47; P = 0.51). The investigators concluded that gingko was not effective in preventing incident AD.

In conclusion, there is little evidence to support the use of gingko biloba to delay the onset of Alzheimer's disease.

Omega-3 fatty acids. We identified two good quality systematic reviews evaluating the association between omega-3 fatty acids and risk of Alzheimer's disease[29,31] The Cochrane review by Lim et al.[31] searched multiple databases for randomized, double-blinded, placebo-controlled trials lasting at least 6 months in persons aged 60 or above without pre-existing dementia. Through October 2005, no eligible studies were identified. Fotuhi et al.[29] searched for trials that addressed the specific association between any form of omega-3 fatty acids in participants age 65 or older and used standard diagnosis of dementia. No trials were identified. Our independent search also failed to identify any relevant studies.

Other fats. We identified no RCTs of other fats used to delay the onset of AD.

Trace metals. We identified no RCTs evaluating the use of trace metals to delay the onset of AD.

Mediterranean diet. We identified no RCTs evaluating the use of a Mediterranean diet to delay the onset of AD.

Intake of fruits and vegetables. We identified no RCTs assessing the relationship between fruit and vegetable intake and onset of AD.

Total intake of calories, carbohydrates, fats, and proteins. We identified no RCTs evaluating the relationship between total intake of calories, carbohydrates, fats, and protein and onset of AD.

Medical Factors

Medications. Prescription and non-prescription drugs considered under this heading include statins, antihypertensives, anti-inflammatories, gonadal steroids, cholinesterase inhibitors, and memantine.

Statins. No systematic reviews or RCTs were identified evaluating the effects of statins on the incidence of AD.

Antihypertensives. We identified one good quality systematic review evaluating the association between antihypertensive medications and the prevention of dementia.[34] Our own independent search did not identify any additional studies. Included in the systematic review were randomized, double blind, placebo-controlled trials whose subjects had a diagnosis of hypertension without clinical evidence of cerebrovascular disease. Three trials, SCOPE, Syst-Eur and SHEP were included.[374-376] SCOPE randomized participants (who had an entry SBP of 160 to 179 mmHg or a DBP 90 to 99 mmHg or both) in a 1:1 ratio to placebo or candesartan. There was a stepwise progression of medication changes based on blood pressure. SHEP included subjects with isolated systolic hypertension (SBP 160 to 219 mmHg, DBP < 90 mmHg). Participants were randomized to placebo or chlorthalidone, with atenolol or reserpine added if necessary. Syst-Eur also enrolled subjects with isolated systolic hypertension. SBP was 160 to 219 mmHg at entry, with DBP < 95 mmHg. Subjects were randomized to placebo with medications added if SBP remained high versus nitrendipine with addition of enalapril and/or hydrochlorothiazide. All studies reported rates of incident dementia, but only one[376] reported the proportion of patients with AD, and only a total of 23 cases were observed. In all studies, cognitive outcomes were a secondary outcome and investigators did not report a priori sample

size calculation specific to this outcome. Given the low rate of incident dementia, these studies may have been underpowered to detect clinically important differences between interventions.

All studies had a significant number of control-assigned subjects on active medication (84 percent in SCOPE, 27 percent in Syst-Eur during study, and 44 percent in SHEP). This treatment contamination would decrease differences between groups. Also, in each study, a minority of subjects was taking initially assigned medications (25 percent in SCOPE, 30 percent in Syst-Eur, 30 percent in SHEP). All studies did achieve a differential BP response, with lower pressures in subjects assigned to active treatment (differences for SBP/DBP were SCOPE 3.2/1.6 mmHg, SHEP 11.1/3.4 mmHg, and Syst-Eur 10.1/4.5 mmHg). In a meta-analysis, treatment with antihypertensives did not decrease the risk for general dementia (OR 0.89; 95 percent CI 0.69 to 1.16).

Forette and colleagues[376,377] followed the Syst-Eur subjects for an additional 2 years after the end of the study. All control subjects who wished to continue were changed to active medication at that time. Throughout the followup, blood pressure remained lower in the group initially assigned to active treatment by 7.0 mmHg/3.2 mmHg. In spite of the majority of subjects being on active treatment, the rates of dementia were lower in the active treatment group. The reasons for the decrease in incidence of dementia are not known. Nitrendipine, a calcium channel blocker, was the first study drug started and showed a HR of 0.38 (95 percent CI 0.23 to 0.64). It may be that the subjects opting not to continue in the trial had a higher rate of cognitive decline, biasing results away from a null effect. It is noted that there was a protective effect in the Syst-Eur study during the duration of the trial also (incidence decreased by 50 percent from 7.7 to 3.8 cases per 1000 patient-years).[34,376,377]

In summary, a combination of three large, multi-site RCTs did not suggest a protective effect of antihypertensive treatment in incident dementia. The proportion of subjects with incident AD was not consistently reported, so the applicability of these data to our study question is uncertain. The trials are difficult to evaluate, as many patients were lost to followup and many subjects assigned to the control group received medications when their blood pressure remained elevated. Bias could be introduced via both mechanisms. It also is noted that durations of studies were fairly brief (5 years), and that all studies looked at non-specific dementia rather than AD. The brief followup study to Syst-Eur did suggest a benefit to antihypertensives, but in this open-label continuation study all subjects were receiving active treatment. Details of dementia diagnosis are limited, and it is possible that subjects with cognitive impairment would be less likely to participate in the followup study.

Anti-inflammatories. Our search identified two RCTs using NSAIDs and reporting AD as an outcome. Both studies invoked early stopping rules. Thal et al.[378] evaluated subjects who had MCI at baseline. A total of 1457 subjects with a MMSE $\geq$ 24 were randomized to rofecoxib 25 mg daily, a drug that subsequently was withdrawn from the market due to safety concerns, or placebo. The study was powered based on the projection of 220 incident cases of AD. The original 2-year study duration was lengthened to 4 years because of lower than expected conversion rates, and was then shortened to approximately 3 years, as reaching the goal was determined to be futile. Over the course of the study 189 subjects developed AD by the study definition, primarily a Clinical Dementia Rating Scale (CDR) score $\geq$ 1, which triggered further evaluation. A minority of subjects actually completed the study on drug (40 percent of the rofecoxib group and 41 percent of the placebo group). The most common reasons for discontinuation were withdrawal of consent, followed by adverse events, and then subjects who were lost to followup, uncooperative, or moved. A "completers" analysis evaluating those

subjects who finished the study on drug showed an increased risk of AD with NSAIDs (HR 1.49; 95 percent CI 1.08 to 2.05), as did the intention-to-treat analysis (HR 1.46; 1.09 to 1.94).

The second trial, by the Adapt Research Group,[379] randomized 2528 subjects who were first-degree relatives of AD patients to using celecoxib, naproxen, or placebo. Subjects received cognitive testing at baseline, and those scoring low enough were referred for a more comprehensive dementia evaluation. The cut-points used to trigger a full evaluation were not reported. This study was closed early because of concerns over the safety of COX-2 inhibitors as a class. Poor adherence to study medications was common: 83 to 85 percent of subjects had sufficient data to be included in analysis, but almost half of subjects had terminated use of the study drug. According to subject reports, the active medications were taken on medians of 546 and 561 days out of a possible 733 days. Seven demented subjects were inadvertently enrolled. When the data from these subjects were excluded, there were 5 subjects who developed AD in the placebo group, 11 in the celecoxib group, and 9 in the naproxen group. Reflecting the small number of cases, the confidence intervals were large: the HR for celecoxib versus placebo was 4.11 (95 percent CI 1.30 to 13.0), and the HR for naproxen versus placebo was 3.57 (1.09 to 11.7).

In summary, both RCTs suggest that NSAIDs increase the risk of incident AD. Explanations are not clear, but it is possible that NSAIDs adversely affect cognition. Alternatively, initiation of an anti-inflammatory after MCI has manifested itself may be too late in the course of illness for benefit. Studies that have attempted to treat AD with NSAIDs have also had negative findings, and MCI may well represent a prodrome in many patients. The trial conducted by the Adapt Research Group[379] attempted to begin with unimpaired subjects. The randomization of a small number who had actual dementia casts some doubt on the sensitivity of the screening process. The frequent termination of study drugs may also have introduced some bias, depending on the cause of termination. It has been suggested that cognitively impaired subjects may be more likely to terminate participation in a trial. By subject report, it also appears that those remaining on medication had a cumulative time on NSAIDs of approximately 18 months, less than has been suggested necessary by observational studies.

Gonadal steroids. No good quality systematic review was identified that specifically addressed the therapeutic and adverse effects of gonadal steroids on development of AD. We identified two RCTs involving 7479 women that examined the effect of estrogen with or without progestins on the development of Alzheimer's disease.[380,381] Both studies were conducted in the United States and used a staged diagnosis based on DSM-IV criteria for AD, with data from cognitively impaired individuals referred to a central adjudication committee. Participants were community-dwelling, non-demented, postmenopausal women between the ages of 65 and 79 years recruited from 39 of the 40 Women's Health Initiative Centers. Treatment consisted of conjugated equine estrogen (CEE 0.625 mg) or CEE plus 2.5 mg medroxyprogesterone acetate (MPA) versus placebo. Both studies assessed cognitive function at baseline using the Modified Mini-Mental State Examination (3MS); duration of followup was 4 (CEE plus MPA) or 5 (CEE) years.

The primary outcome in both studies was probable dementia, but a diagnosis of AD was made in half the patients with dementia (54 of 108 cases). An additional 16 percent of cases with dementia (17 of 108) were attributed to a mixture of cerebrovascular and AD (mixed dementia). Results are summarized in Table 69. Treatment with CEE alone did not reduce the risk of probable dementia, but appeared rather to increase it (HR 1.76; 95 percent CI 1.19 to 2.60; P = 0.005). After excluding participants with baseline 3MS scores at or below the screening cut

point, the association of increased risk of dementia with CEE alone was no longer statistically significant (HR 1.77; 95 percent CI 0.74 to 4.23; P = 0.20), suggesting that these subjects may have been cognitively impaired at the time of enrollment in the study. Treatment with CEE plus MPA significantly increased the risk of developing dementia (HR 2.05; 95 percent CI 1.21to 3.48; P = 0.01). No statistics were provided for AD as a separate endpoint in either the CEE or CEE plus MPA treatment arms.

Table 69. Therapeutic effects of gonadal steroids on development of AD

Treatment	HR (95% CI) for probable dementia
CEE	1.76 (1.19 to 2.60); P = 0.005
Exclusion participants with low baseline 3MS	1.77 (0.74 to 4.23); P = 0.20
CEE plus MPA	2.05 (1.21to 3.48) P = 0.01

Abbreviations: 3MS = Modified Mini-Mental State Examination; AD = Alzheimer's disease; CEE = conjugated equine estrogen; CI = confidence interval; HR = hazard ratio; MPA = medroxyprogesterone acetate

The findings from these studies demonstrate that hormone therapy with estrogen with or without progestin does not reduce the risk of dementia in postmenopausal women. Regular use of CEE plus MPA by postmenopausal women slightly increases the risk of dementia.

Our own independent search did not identify any additional studies.

Cholinesterase inhibitors. We identified one good quality systematic review that examined the effects of cholinesterase inhibitors on the progression to dementia or AD.[44] The review included eight RCTs (4127 subjects). Four were multi-site studies in North America or the United States; one was a multi-site study in North America and Western Europe; one was a small, single-site U.S. study; and two did not report location. RCTs were selected that compared a cholinesterase inhibitor (donezpezil, galantamine, rivastigmine) to placebo control in participants with abnormal memory function and/or who met diagnostic criteria for mild cognitive impairment (MCI); individuals with dementia were excluded. Only English-language studies and studies presenting original data were included. Study quality was assessed using the Jadad criteria and was judged to be low to medium. Only one trial adequately described the randomization process; four followed an intention-to-treat principle for analysis; loss to followup was substantial and greater for intervention than control subjects; and in all but one study, multiple secondary outcome measures were evaluated without correction for multiple comparisons. Formal tests for publication bias (e.g., funnel plot) were not performed, but three completed studies[382-384] identified at ClinicalTrials.gov have not reported results, suggesting possible publication bias. One was a 16-week industry-sponsored study of rivastigmine that was terminated early in 2004.[384] The second was a 1-year National Institute of Mental Health-sponsored study of donepezil and gingko biloba extract completed in 2004.[383] The third was a 1-year, industry-sponsored study of donepezil in subjects with MCI completed in March 2007.[382] From the available records, it is unclear if conversion to AD was an outcome measure in these trials.

Of the eight identified trials, four (described in three publications[385-387]) reported rates of conversion to dementia/AD. Cholinesterase inhibitors evaluated were donepezil 10 mg daily, rivastigmine 3 to 12 mg daily, and galantamine 16 or 24 mg daily (two studies). The number of subjects ranged from 769 to 1062. Participants were age ≥ 50 years; race was reported in only one publication, describing two studies,[386] and over 90 percent of subjects were white. One

study[387] recruited subjects with amnestic MCI, while the other studies used more inclusive criteria for MCI. Two studies specifically reported conversion to AD at 3 to 4 years using NINCDS-ADRDA criteria,[385,387] while the other two reported conversion to dementia at 2 years based on an increase in the CDR from 0.5 to 1.0.[386] The authors of the systematic review did not compute a summary estimate of effect due to important heterogeneity in the definition for MCI.

Conversion to dementia or AD for subjects treated with a cholinesterase inhibitor ranged from 13 percent (at 2 years) to 25 percent (at 3 years). In comparison, control subjects converted at a rate of 18 percent (at 2 years) to 28 percent (3 years). Hazard ratios for conversion to AD were reported in two studies and did not show a statistically significant reduction in risk: HRs were 0.85 (95 percent CI 0.64 to 1.12)[385] and 0.80 (0.57 to 1.13).[387] Treatment discontinuation due to adverse events was significantly higher for intervention subjects, ranging from 21 to 24 percent compared to 7 to 13 percent in control subjects. Effects on mortality were not adequately reported. The authors concluded that the use of cholinesterase inhibitors in MCI was not associated with any delay in the onset of AD or dementia, and that the safety profile showed that risks associated with cholinesterase inhibitors are not negligible. A fair quality systematic review[388] evaluated the same four trials and computed a summary estimate showing a decreased risk of conversion to AD or dementia (RR 0.75; 95 percent CI 0.66 to 0.87) and a higher all-cause dropout risk (RR 1.36; 95 percent CI 1.24 to 1.49). We judged these summary estimates to be suspect due to significant variability in the definition of MCI, variability in outcomes (AD versus any dementia), and probable publication bias.

We did not identify any additional trials that evaluated cholinesterase inhibitors and reported conversion to AD or dementia, but we identified a subgroup analysis from the Petersen trial comparing donepezil to placebo in 769 subjects with amnestic MCI and Hamilton Depression Rating Scale (HDRS) scores < 12 (consistent with no current mild to moderate major depressive disorder [MDD]). The primary outcomes publication conducted subgroup analyses in APOE e4 carriers, showing a reduced risk for conversion to AD in patients treated with donepezil (HR 0.66; 95 percent CI 0.44 to 0.98). Benefit in APOE e4 carriers was not demonstrated in subgroup analyses from the study by Feldman et al.[385] The subgroup analysis[42] evaluated the effects of donepezil in subjects with Beck Depression Inventory (21-item) scores ≥ 10, consistent with significant depressive symptoms despite the absence of MDD. In the subgroup with significant depressive symptoms (n = 208), donepezil treatment was associated with a lower conversion to AD at 1.7 years (11 percent versus 25 percent) and 2.2 years (14 percent versus 29 percent), but not at 2.7 years (18 percent versus 32 percent, p = 0.07).

In summary, a systematic review found four low to medium quality trials reporting the effects of cholinesterase inhibitors on conversion to dementia/AD in subjects with MCI. Study heterogeneity precluded a valid summary estimate of effect, but conversion rates were similar in intervention and control subjects. Differential effects in subgroups, including those at higher risk for progression to AD (e.g., amnestic MCI, depressive symptoms, APOE e4) are inconsistent.

Memantine. We did not identify any systematic reviews or primary studies that evaluated the effects of memantine on incident AD in subjects who were cognitively normal or had mild cognitive impairment.

Social, Economic, and Behavioral Factors

We did not identify any good quality systematic reviews or RCTs that evaluated the effects of the following types of interventions for delaying the onset of AD:

- Social engagement;
- Cognitive engagement;
- Physical activities;
- Other leisure activities;
- Nicotine.

Key Question 4 – Interventions to Improve or Maintain Cognitive Ability or Function

Key Question 4 is: What are the therapeutic and adverse effects of interventions to improve or maintain cognitive ability or function? Are there differences in outcomes among identifiable subgroups?

Nutritional and Dietary Factors

B vitamins and folate. We identified two RCTs that examined the effect of B vitamins on maintenance of cognitive function.[389,390] The first[389] was a substudy of a larger ongoing RCT examining the effect of antioxidants and folic acid on reduction of cardiovascular disease in female health professionals throughout the United States. Those included in the parent study were at least 40 years of age, had at least three coronary disease risk factors, completed the run-in-phase of the RCT adequately, were willing to forgo use of other vitamin supplements during the course of the study, and had no history of cancer, active liver disease, chronic kidney failure, or use of anticoagulants. The cognitive substudy was limited to participants in the parent RCT who were aged 65 years and older. No details were provided regarding the baseline cognitive status of participants, but since these individuals were part of an ongoing RCT for cardiovascular disease, one would predict that the vast majority were non-demented at baseline. This substudy included participants assigned to one of the treatment arms and a placebo group of the parent study. The intervention was a daily combined vitamin of 2.5 mg folic acid, 50 mg vitamin B6, and 1 mg vitamin B12. The time from randomization to the intervention and end of the trial was 6.6 years. The initial cognitive assessment was about 1 year after the start of the intervention, and assessments were then repeated about every 2 years for a total of four assessments. Cognitive function was measured using a telephone assessment protocol that included the Telephone Interview for Cognitive Status (TICS), an immediate and delayed verbal memory task, and a semantic fluency task. The primary outcome measures were: longitudinal change on a global composite score that was derived by combining scores from all cognitive tests; and longitudinal change on a memory composite score that was derived by combining the memory measures.

Of the 2164 individuals meeting inclusion criteria for the substudy, 93 percent (2009) completed the first cognitive assessment. Ninety-four percent completed at least one followup

assessment, and 83 percent completed at least three cognitive assessments. Cumulatively, however, just over 50 percent of the sample completed the final followup assessment (4th assessment) due primarily to the short interval of time between the third cognitive assessment and the RCT end date. Participation rates did not differ by treatment group. Compliance with treatment was 83 percent for both the intervention and placebo groups. The main independent variable was the treatment arm (intervention versus placebo). There was no difference in cognitive decline over time between the intervention and placebo groups. The mean difference in cognitive decline over time between the treatment and placebo groups was 0.03 standard units per year (95 percent CI -0.03 to 0.08; p = 0.30) for the global score and 0.03 (95 percent CI -0.03 to 0.09; p = 0.36) for the verbal memory score. However, in subgroup analyses the investigators examined whether other possible risk factors for cognitive decline modified the effect of the treatment and placebo groups on rates of cognitive change. One of the potential effect modifiers was dietary intake of vitamin B6 and B12 and folate based on self-reported responses to a semi-quantitative food-frequency questionnaire administered at baseline. The results of these subgroup analyses showed that there was no difference in rate of cognitive change for the global cognitive score or the global memory score when stratified by estimated levels of dietary intake of B vitamins or folate. However, the analyses provided some support for the idea that supplemental B vitamins and folate may be advantageous in maintaining cognitive performance on the TICS for those with low dietary intake of B vitamins and folate.

In summary, this cognitive substudy of a larger RCT found no association between supplemental B vitamins and folate and rate of cognitive change over a period of about 6 years. The substudy used assignment to the treatment or placebo group as the predictor variable and did not use serum levels of the B vitamins or folate.

The second RCT[390] investigated the effect of combined folate, B6, and B12 supplementation on cognition (primary outcome) and homocysteine levels (secondary outcome) among individuals with elevated baseline homocysteine levels. The study was conducted in New Zealand. Participants were recruited from service clubs. Inclusion criteria included age 65 and older, a fasting homocysteine > 13 μmol/L, and a normal creatinine level. Exclusion criteria were suspected dementia; taking medications known to interfere with folate metabolism (e.g., oral hypoglycemic agents or antiepileptic agents); taking vitamin supplements containing folic acid, vitamin B12, or vitamin B6; being treated for depression; diabetes; or a history of stroke or transient ischemic attacks. The participants were randomized to either the treatment arm (one capsule per day that contained 1000 μg of folate, 500 μg of vitamin B12, and 10 mg of vitamin B6) or the placebo group (one placebo capsule per day). The trial lasted for 24 months and had three time points of cognitive testing (baseline, 1 year, and 2 years). Of the 276 individuals randomized in the trial, 253 (92 percent) completed the study and were included in the analyses. This included 15 individuals who discontinued taking the supplement, but completed all cognitive testing. Compliance rate was adequate, as 85 percent of participants took 95 percent of the supplements. The cognitive battery included a number of standard neuropsychological measures for the assessment of cognitive decline in later life and assessed a range of cognitive domains including memory, verbal fluency, executive function, reasoning, and orientation. Scores were reported for individual tests and also for a standardized combined score for all tests. Change in performance on the cognitive measures over time was calculated controlling for age, sex, and baseline cognitive score.

We note that the study authors interpreted the results as showing overall no significant differences in cognitive performance for the treatment and placebo groups. However, the results

showed a modest but statistically significant difference ($p = 0.05$) in the summary cognitive score, with the treatment group scoring 0.11 standard deviations lower than the placebo group. Analysis of change in individual test scores revealed a statistically significant worsening of scores on Trails B in the treatment group as compared to the placebo group (the exponent of the difference between the log-transformed values is the ratio of the result in the vitamin group compared to the placebo group = 1.08; 95 percent CI 1.02 to 1.14). The treatment group tended to show greater decline on most of the cognitive measures, but these differences did not meet standard statistical significance levels.

The secondary outcome of homocysteine levels showed that the vitamin group had homocysteine levels that were, on average, 4.36 μmol/L ($p < 0.001$) lower than the placebo group.

In summary, the two RCTs that have examined the effect of supplemental folate and vitamins B6 and B12 on maintenance of cognition in later life have not shown a beneficial effect.

Other vitamins. We identified five RCTs that examined the effect of supplemental vitamin E, vitamin C, or a multivitamin on maintenance of cognitive function.[372,391-394] The studies are summarized here, and further details are provided in evidence tables in Appendix B. The first trial[392] was a substudy of the Women's Health Study that examined the effect of vitamin E and low-dose aspirin on the prevention of cardiovascular disease and cancer. Inclusion criteria for the parent study were women at least 45 years old; no history of coronary heart disease, cerebrovascular disease, cancer (except for non-melanoma skin cancer), or other major chronic illnesses; not actively using any of the study medications; and no history of adverse effects from any study medications. The cognitive substudy was limited to women age 65 and older and began about 5.6 years after randomization for the parent study. A detailed description of the participants' baseline cognitive status was not provided, but based on the mean baseline scores on the TICS, the majority of participants were likely non-demented at baseline. The intervention group took vitamin E (600 IU) and low-dose aspirin (100 mg) every other day; the placebo group took a placebo pill on the same schedule. Of the 7175 eligible for the study, 6377 (89 percent) completed the baseline cognitive assessment, and 5073 completed all three cognitive assessments. Followup rates did not differ for the treatment and placebo groups. Compliance was similar for the two groups, as 75.4 percent of the vitamin E group and 76.9 percent of the placebo group reported taking at least two-thirds of the assigned pills. The cognitive substudy lasted for 4 years, which included three telephone cognitive assessments at 2-year intervals. The assessment included five tests measuring general cognition, verbal memory, and category fluency. The primary outcome was longitudinal change on a global composite score derived by averaging standardized scores across all five tests.

The findings showed that there was essentially no difference in rates of cognitive decline between the two groups. Mean cognitive change over time was similar in the vitamin E group compared with the placebo group for the global score (mean difference in change = 0.00; 95 percent CI -0.04 to 0.04). The relative risk of substantial decline in the global score in the vitamin E group compared with the placebo group was 0.92 (95 percent CI 0.77 to 1.10). (Relative risk < 1.0 means vitamin E was associated with lower risk of substantial decline). There were no statistically significant differences in cognitive change between the treatment and placebo group for the secondary outcomes of longitudinal performance on the individual cognitive tests.

The second RCT[391] examined the effect of micronutrient supplementation on maintenance of cognition. This was a secondary outcome of the MAVIS (Mineral And Vitamin Intervention

Study) trial, which was a large RCT of multivitamin and multimineral supplementation designed to assess possible effects on infection in men and women aged 65 years or over using a supplement containing 11 vitamins and 5 minerals. Participants were recruited from six primary care clinics in northeast Scotland. Participants had to have not taken vitamin, mineral, or fish oil supplements within 3 months of recruitment (1 month for supplements of water soluble vitamins other than vitamin B12). The cognitively impaired were not overtly excluded, although the authors noted that individuals with dementia were unlikely to volunteer to participate or would have been excluded by their physician. A total of 910 individuals enrolled in the study and were randomized. Over the 12-month study, the dropout rates were 12.7 percent for the treatment group and 17.6 percent for the placebo group. The treatment group daily took a multivitamin composed of 16 vitamins and minerals at one to two times the recommended daily allowance. The placebo group took a placebo pill on the same schedule. Compliance with taking the tablets was over 78 percent in both supplemented and placebo groups. The cognitive assessment included the Digit Span forward test and a phonemic verbal fluency measure. The tests were administered in person at the beginning of the study and then by telephone at the end of the study.

The results of the study showed no differences in cognitive change between the treatment and the placebo groups, either in the groups as a whole or in analyses of the over age 75 subgroup or the subgroup at risk for micronutrient deficiency (as defined by self-report responses to a food frequency questionnaire). The different modes of test administration at baseline (in person) and the end of the study (telephone) may have increased the variability in performances over time, but this was unlikely to differ between treatment and placebo groups.

The third RCT[372] examined the association between vitamin E supplementation and decline on cognitive tests and other cognitive/functional outcomes over a 3-year period among individuals with amnestic MCI. These were secondary outcomes to the RCT described under Question 3; details of the study are described in that section. Every 6 months during the 3-year trial, a range of standard cognitive tests were completed in addition to the Clinical Dementia Rating scale, the Activities of Daily Living Scale, and the Global Deterioration Scale. Among the numerous outcomes assessed, there were few significant differences between the treatment and placebo groups. The significant differences were less decline in the vitamin E treatment group on measures of executive function ($p < 0.05$) and overall cognitive score at the 6-month assessment, and on language measures ($p < 0.5$) up through the 18-month assessment. No significant differences remained after 18 months.

The fourth RCT[393] examined the association between an antioxidant vitamin and cognitive decline over a 1-year period. Participants were recruited using advertisements in the United Kingdom. Inclusion criteria were age between 60 and 80 years; within two standard deviations of the normal weight for height, age and sex; no history of significant disease or mental illness; able to give informed consent; and capable of taking 80 ± 120 percent of the prescribed number of capsules during the run-in period. Exclusion criteria were: current medication likely to influence the outcome measures; use of vitamin supplements in the preceding 3 months; history of drug abuse, including alcohol; significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, neurological disease or abnormality; malabsorption syndrome; psychiatric disorder; subjects unable to give informed consent; disorders which would interfere with the understanding or compliance with the study, hypersensitivity to any of constituents in the active treatment; MMSE score < 18; participation in another drug clinical trial within the previous 6 months; and subjects from whom blood samples could not be obtained. The exclusion criteria

would have excluded individuals with dementia of moderate or greater severity; however, it is possible that some individuals with mild dementia were included. There was a treatment and a placebo group. The treatment group took a vitamin containing 2 mg beta carotene, 400 mg alpha-tocopherol, and 500 mg ascorbic acid daily. No information was provided on whether the outcome assessors or the participants were blind to group assignment. A total of 205 subjects were randomized; 185 appeared to have completed all assessments, but few details were provided. Participants were assessed at baseline and at 4, 8, and 12 months thereafter. The cognitive assessment included measures of verbal memory, logical reasoning, attention, and reaction time. The analyses for the study did not adjust for baseline cognitive performance. The authors reported the number of significant findings on all cognitive measures did not exceed the number one would expect to find by chance (4/117 significant). The actual significance levels were not reported for any of the measures.

The fifth and final RCT[394] was a substudy of a larger ongoing RCT examining the effect of antioxidants and beta carotene on reduction of cardiovascular disease in female health professionals throughout the United States. Those included in the parent study were at least 40 years of age, had at least three coronary disease risk factors, completed the run-in phase of the RCT adequately, were willing to forgo use of other vitamin supplements during the course of the study, and had no history of cancer, active liver disease, chronic kidney failure, or use of anticoagulants. The cognitive substudy was limited to participants in the parent RCT who were aged 65 years and older. No details were provided regarding the baseline cognitive status of participants, but since these individuals were part of an ongoing RCT for cardiovascular disease, one would predict that the vast majority were non-demented at baseline. This substudy included participants assigned to one of the treatment arms and a placebo group of the parent study. The intervention was three antioxidants: 420 mg vitamin E every other day, 500 mg vitamin C daily, and 50 mg beta carotene every other day. There were eight intervention groups that ranged from zero to three active vitamins. The time from randomization to the intervention and end of the trial was 8.9 years. The initial cognitive assessment was about 3.5 years after the start of the intervention, and assessments were then repeated about every 2 years for a total of four assessments. Cognitive function was measured using a telephone assessment protocol that included the TICS, an immediate and delayed verbal memory task, and a semantic fluency task. The primary outcome measures were: longitudinal change on a global composite score that was derived by combining scores from all cognitive tests; and longitudinal change on a memory composite score that was derived by combining the memory measures.

Of the 3170 individuals meeting inclusion criteria for the substudy, 89 percent (2824) completed the first cognitive assessment. Ninety-one percent completed at least one followup assessment, and 81 percent completed at least three cognitive assessments. The number of participants who completed the 4th assessment was not given, but the study authors stated that 24 percent of the sample was not contacted for the final followup assessment due to the short interval of time between the third cognitive assessment and the RCT end date. Participation rates did not differ by treatment group. Compliance with the treatment, defined as taking at least two thirds of the study pills, ranged from 64 to 68 percent and was comparable across all groups. The main independent variables were the various treatment arms (intervention versus placebo). The primary outcome was a global composite score averaging all scores; repeated-measures analyses were used to examine cognitive change over time.

Results showed that vitamin E supplementation and beta carotene supplementation were not associated with slower rates of cognitive change (mean difference in change for vitamin E versus

placebo -0.01 standard unit; 95 percent CI -0.05 to 0.04; P = 0.78; for beta carotene, 0.03; -0.02 to 0.07; P = 0.28). Although vitamin C supplementation was associated with better performance at the last assessment (mean difference 0.13; 95 percent CI 0.06 to 0.20; *P*=0.0005), it was not associated with cognitive change over time (mean difference in change 0.02; 95 percent CI -0.03 to 0.07; P = 0.39). In secondary analyses, those taking at least one of the three antioxidant supplements (n = 2471) did not differ in cognitive change from baseline compared with those assigned to all placebos (n = 353); mean difference in cognitive change over time was 0.02 standard units (95 percent CI -0.04 to 0.09; P = 0.64). A number of other secondary analyses were done to examine whether the results differed by various subgroups. One result from these secondary analyses was the finding that vitamin C supplementation was associated with better performance over time among those who developed cardiovascular events during followup (difference in change from baseline in global score for vitamin C group versus placebo 0.15; 95 percent CI 0.04 to 0.26) compared to those who did not experience new cardiovascular events (difference in change 0.00; 95 percent CI, -0.05 to 0.05; P for interaction = 0.009). The authors of the study concluded that vitamin E, vitamin C, or beta carotene supplementation was not associated with less cognitive decline in women with cardiovascular disease or risk factors.

In conclusion, the five included RCTs do not provide support for a beneficial effect of supplemental vitamin E, vitamin C, or a multivitamin on maintenance of cognitive function.

Gingko biloba. We identified one RCT that examined the effect of gingko biloba on maintenance of cognitive function.[395] Participants were recruited through mass mailings to individuals on public registry lists in Oregon. Inclusion criteria were: over 84 years of age; no subjective complaint of memory impairment compared to others of similar age; has not sought assessment for memory or cognitive dysfunction; normal memory based on performance on specific cognitive tests; functionally independent; not depressed; adequate vision and hearing to complete all testing; adequate English language skills to complete all testing; general health status that will not interfere with ability to complete longitudinal study; and informant available with frequent contact with subject to verify functional status. Exclusion criteria were: diseases associated with dementia or significant cognitive impairments, current alcohol or substance abuse, B12 deficiency, thyroid disease, or urinary tract infection. The trial lasted for 42 months. The treatment group took 80 mg of gingko biloba three times per day, and the placebo group took a placebo pill on the same schedule. All subjects also took a daily multivitamin with 40 IU of vitamin E. Two outcomes that were examined were incident mild cognitive decline, defined as progression from Clinical Dementia Rating Scale Score (CDR) = 0 to CDR = 0.5, and decline in memory function over time measured by performance on a verbal recall delayed memory task.

A total of 134 participants were enrolled and randomized in the trial, of which 118 (88 percent) met completion criteria and were included in the analyses. The dropout rate did not differ between the treatment and the placebo groups. The assessment included an in-person interview and cognitive status screening every 6 months and more comprehensive neuropsychological testing annually. The maximum number of assessments was seven. Overall, 68.6 percent of participants met the definition of medication compliance, and the gingko biloba group (65.0 percent) did not differ from the placebo group (72.4 percent).

The results showed that in the intention-to-treat analysis there was no reduced risk of progression to a CDR score of 0.5 (HR 0.43; 95 percent CI 0.17 to 1.08) in the gingko biloba group. There was also no less of a decline in memory function in the treatment group (coefficient [SE] 0.111 [0.057]; p = 0.055). In the secondary analysis that controlled for the medication adherence level, the gingko biloba group had a lower risk of progression from a CDR score of 0

to 0.5 (HR 0.33; 95 percent CI 0.12 to 0.89) and a smaller decline in memory scores (coefficient [SE] = 0.115 [0.057]; p = 0.047). The study authors noted that a larger RCT was needed to clarify whether gingko biloba was advantageous in deterring cognitive decline, especially among those compliant with the medication use.

In conclusion, there is little evidence to support the use of gingko biloba to improve or maintain cognitive ability or function.

Omega-3 fatty acids. We identified a single good quality systematic review evaluating the use of omega-3 fatty acids to improve or maintain cognitive ability or function.[29] The authors searched for trials that addressed the specific association between any form of omega-3 fatty acids and cognitive decline in participants age 65 or older. Four trials were identified, but three were conducted in subjects with dementia or organic brain lesions. A single 26-week trial compared DHA-EPA 400 mg or 1800 mg versus placebo in adults age ≥ 65 with MMSE score > 21 at baseline.[396] There was no statistically significant effect for any of the four cognitive domains evaluated. Four ongoing RCTs[397-400] were identified evaluating the effects of omega-3 fatty acids in mid-life to older adults without dementia. Study recruitment has been completed in three of the four studies, but results had not been published at the time of our search.

Other fats. We identified no RCTs of other fats used to improve or maintain cognitive ability or function.

Trace metals. We identified no RCTs assessing the relationship between trace metals and cognitive decline. We did identify one RCT[391] that assessed the association between multivitamins (which included trace metals) and cognitive function; this study is described above, under "Other vitamins."

Mediterranean diet. We identified no RCTs of the Mediterranean diet used to improve or maintain cognitive ability or function.

Intake of fruits and vegetables. We identified no RCTs assessing the relationship between fruit and vegetable intake and improvement or maintenance of cognitive ability or function.

Total intake of calories, carbohydrates, fats, and proteins. We identified no RCTs evaluating the relationship between total intake of calories, carbohydrates, fats, and protein and improvement or maintenance of cognitive ability or function.

Medical Factors

Medications. Prescription and non-prescription drugs considered under this heading include statins, antihypertensives, anti-inflammatories, gonadal steroids, cholinesterase inhibitors, and memantine.

Statins. A good quality systematic review examined the effects of two HMG-CoA reductase inhibitors (statins) on cognitive decline[33] The review included two trials that randomized participants to a statin or placebo for the primary purpose of examining effects on cardiovascular events.[401,402] Change in cognitive status and adverse events were secondary outcomes. The two trials randomized 26,340 adults from Western Europe, aged 40 to 82 years old, at elevated risk for vascular events. A summary estimate of effect was not computed because the cognitive outcomes and duration of followup varied significantly. Both studies were assessed overall as good quality.

The Heart Protection Study[401] (n = 20,536) excluded individuals with a history of dementia but did not assess cognition at baseline; a modified Telephone Interview for Cognitive Status (TICS-m) score below 22 of 39 was pre-specified as indicating cognitive impairment.

Participants were randomized to simvastatin (40 mg daily), a lipophilic statin, or matching placebo. Adherence was reported as 85 percent; 17 percent of the placebo group used a non-study statin. Mean duration of followup was 5 years, and the followup rate was high. The proportion of subjects with cognitive impairment at final followup did not differ between treatment (23.7 percent) and placebo groups (24.2 percent, p = not significant). The unadjusted difference in mean TICS-m scores did not differ significantly (24.08 simvastatin versus 24.06 placebo; difference = 0.02 [SE 0.07]). Discontinuations due to adverse events were similar (4.8 percent simvastatin versus 5.1 percent placebo). Key methodological limitations are the limited cognitive outcomes and the lack of a baseline cognitive assessment.

The PROSPER study[402] (n = 5806) excluded individuals with a MMSE < 24; changes in scores on four cognitive tests were reported. Participants were randomized to pravastatin (40 mg daily), a hydrophilic statin, or matching placebo. Adherence was reported as 94 percent; 10 percent of the placebo group used a non-study statin. Mean duration of followup was 3.2 years; approximately 25 percent of participants in each group withdrew. Cognitive status – including global cognition, cognitive speed, and cognitive inhibition – was measured by MMSE, picture-word learning test, Stroop Color-Word Test, and a letter digit coding test. Changes in cognition adjusted for age, SBP, body mass index, alcohol use, concomitant drugs, Barthel Index score, Instrumental Activities of Daily Living (IADL) score, sex, smoking diabetes mellitus, vascular disease, country, and test version (if applicable) did not differ significantly for any of the cognitive assessments. Discontinuations due to adverse events were similar (3.7 percent pravastatin versus 3.98 percent placebo). However, new cancer diagnoses were higher for the pravastatin-treated group (HR 1.25; 95 percent CI 1.04 to 1.51). The study authors completed a meta-analysis of eight randomized placebo-controlled trials lasting at least 3 years which did not show an association between statin use and cancer (HR 1.02; 0.96 to 1.09).

Our search did not identify any additional trials. In summary, two large RCTs conducted in mid- to late-life adults at high risk for vascular disease did not show an effect on cognitive function of statins taken for 3 to 5 years.

Antihypertensives. A good quality Cochrane systematic review[34] evaluated the effects of antihypertensive medications on cognitive impairment (CI) and dementia. In addition to the systematic review, we identified five additional manuscripts discussing several secondary analyses related to the trials in the included review, and two additional trial excluded from the review.[273,374,375,403-406]

Included and discussed in the McGuiness review[34] were three randomized, double blind, placebo-controlled trials whose subjects had a diagnosis of hypertension without clinical evidence of cerebrovascular disease: SCOPE,[374] SHEP,[375] and Syst-Eur.[376] SCOPE randomized participants (who had an entry SBP of 160 to 179 mmHg or a DBP 90 to 99 mmHg or both) in a 1:1 ratio to placebo or candesartan. There was a stepwise progression of medication changes based on blood pressure. SHEP included subjects with isolated systolic hypertension (SBP 160 to 219 mmHg, DBP < 90 mmHg). Participants were randomized to placebo or chlorthalidone, with atenolol or reserpine added if necessary. Syst-Eur also enrolled subjects with isolated systolic hypertension. SBP was 160 to 219 mmHg at entry, with DBP <95 mmHg. Subjects were randomized to placebo, with medications added if SBP remained high, versus nitrendipine with addition of enalapril and/or hydrochlorothiazide.

All studies in the systematic review had a significant number of control subjects taking active medication (84 percent in SCOPE, 27 percent in Syst-Eur during study, and 44 percent in SHEP). This treatment contamination would decrease differences between groups. Also in each

study, a minority of subjects was taking initially assigned medications (25 percent in SCOPE, 30 percent in Syst-Eur, 30 percent in SHEP). All studies achieved a differential BP response, with lowered pressures in subjects assigned to active treatment (differences were SCOPE 3.2/1.6 mmHg, SHEP 11.1/3.4 mmHg, and Syst-Eur 10.1/4.5 mmHg). Cognitive outcomes were secondary analyses in all three studies. Sample size calculations for cognitive decline were reported for SHEP but not SCOPE. Sample size calculations reported for Syst-Eur were for nonspecific dementia only.

In the discussion that follows, we review the secondary analyses identified in our search. In SCOPE, for ethical reasons 84 percent of placebo patients received antihypertensive medications. One publication[407] examined only those subjects without add-on therapy, a comparison that would be expected to amplify any observed treatment benefit. Change in MMSE scores did not differ between placebo and candesartan groups.

Saxby et al.[403] analyzed information from one site of the SCOPE study using a computerized test set to define cognitive decline. As in other sites and trials, there was considerable contamination of allocated groups. At this site, 81 percent of control subjects were on active antihypertensive by study's end, while 68 percent of treatment group was off of assigned medications at study's end. At the study's close the average difference in BP was 8 mmHg/3 mmHg. Small beneficial effects associated with antihypertensive use were seen on episodic memory and attention, but not on speed of cognition, working memory, or executive function.

In SHEP, which included only patients with isolated systolic hypertension, use of add-on medications was common. Add-on medication was triggered by high blood pressure and was more common in the placebo than treatment groups, possibly biasing the results towards a null effect. There was no apparent protective effect of antihypertensives. Di Bari and colleagues[408] also suggest that differential dropouts may have hidden a protective effect of antihypertensives.

The Medical Research Council's (MRC) trial[405] was not included in the systematic review but met our eligibility criteria. This study randomized older adults in a 2:1:1 ratio to placebo, atenolol 50 mg, or hydrochlorothiazide 25 mg. Patients had SBP 160 to 209 mmHg and mean DBP < 115 mmHg during 8 weeks preceding randomization. The mean fall in SBP was 16.4 mmHg in the placebo group, 30.9 mmHg in the atenolol group, and 33.5 mmHg in the hydrochlorothiazide group. A variable proportion of subjects in all treatment arms received additional medications: 20 percent of the hydrochlorothiazide group, 27 percent of the atenolol group, and 1.3 percent of the placebo group. Non-adherence to study medications was substantial; 43 percent of the hydrochlorothiazide group, 52 percent of the atenolol group, and 51 percent of the placebo group were off of allocated treatment for at least part of the 54-month long trial. Cognitive outcomes were assessed using the paired associate learning test and the Trails Making Test, Part A (Trails A). There was no difference in cognitive outcomes based on group assignment.

The PROGRESS study[406] was excluded from the McGuinness systematic review[34] because all subjects had a history of stroke or transient ischemic attack. There were no blood pressure requirements for inclusion. Subjects were randomly assigned to either active treatment with perindopril (plus indapamide if there was neither an indication for nor a contraindication to a diuretic) or a placebo. During the study, 22 percent of subjects discontinued study medication. Cognitive decline was defined by change in MMSE over a mean of 3.9 years of followup. Active treatment was associated with decreased risk for cognitive decline when decline was defined as a drop of ≥ 3 points on the MMSE (RR 0.81; 95 percent CI 0.68 to 0.96). Sensitivity analysis defining cognitive decline as ≥ 2 or ≥ 4 points did not "materially alter" the results. The mean

difference between randomized groups in decline in MMSE score (placebo minus active) was 0.19 (0.07 SE), with less decline for active treatment (p = 0.01).

In summary, participants in these trials had mean ages ranging from 70 to 77 years, except for the PROGRESS trial, where mean age at baseline was 64 years. For individuals with hypertension, antihypertensives were not demonstrably protective against cognitive decline over 4.5 to 5 years. However, all studies had large amounts of treatment contamination and subjects lost to followup. A single trial in subjects with known vascular disease suggests possible benefit with antihypertensive treatment.

Anti-inflammatories. We identified three randomized, placebo-controlled trials evaluating the effects of NSAIDs on cognitive decline. Two studies[409,410] randomized 6244 subjects to 100 mg acetylsalicylic acid (ASA) daily or on alternate days versus placebo for 5 to 6 years. From the trial by Price et al.,[409] only the cognitive change subset, which included 399 subjects, met our inclusion criteria. Within this subset, 24.8 percent of the aspirin group (n = 63) and 16.8 percent of the placebo group (n = 42) were lost to followup. Cognitive outcomes were assessed using a summary score from multiple measures of cognition. Over the 5-year followup, there was no statistically significant difference in cognition (adjusted mean difference 0.01; 95 percent CI -0.07 to 0.09).

The Women's Health Study[410] involved 5845 subjects who had completed at least two cognitive assessments. The authors analyzed this study as a cohort study within the context of an RCT. The trial was originally formed to examine the impact of aspirin on cardiovascular disease and cancer. In the aspirin and placebo groups, 79 and 80 percent of subjects, respectively, completed all three assessments. The cognitive cohort was started at a mean of 5.6 years after randomization, and only women 65 years of age and older were included.

This study found a slower decline in verbal fluency in the aspirin group, but not an effect on the global summary score. Category fluency (number of animals named in a minute) had a mean of 17.76 (SE 0.10) for the aspirin group at third assessment, and a mean of 17.38 (0.10) for the placebo group at the same assessment; the mean difference between the two groups was 0.37 (95 percent CI 0.10 to 0.65). The mean difference between aspirin and placebo groups for the global summary score at the third assessment was 0.00 (95 percent CI -0.04 to 0.04).

The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)[411] randomized 2528 subjects to celecoxib 200 mg two times per day, naproxen 220 mg two times per day, or placebo. This 2-year study terminated early and had a high dropout rate and poor medication compliance. There was a suggestion of worsening with both active drugs. The global summary score was significantly worse only with naproxen. Actual time on drug, as reported by the subjects, averaged 1.50 years for celecoxib and 1.42 years for naproxen.

In summary, there was no effect of low-dose aspirin on cognitive decline in these studies. There was worsening over time with naproxen versus placebo, but not celecoxib versus placebo, in the one RCT available. This study had a high dropout rate, and the actual time on drug was brief. There is no support in these studies for the use of NSAIDs to slow or prevent cognitive decline. As with the incident dementia analysis, the ADAPT study[411] gives some concern for possible worsening of cognitive functioning, but the problems in the trial mitigate this concern.

Gonadal steroids. We identified a single good quality systematic review that examined the effects of gonadal steroids on cognitive function.[37] Studies were included if they were double-blind RCTs that examined the effects of estrogen or estrogen plus progestin on cognitive function over a treatment period of at least 2 weeks in postmenopausal women. Twenty-four studies were included in the review, but only 16 had analyzable data (10,114 women). Eleven

studies were from the United States, seven from Europe, three from Canada, and one from Australia. Treatment duration ranged from 2 weeks to 5.4 years, and five studies had duration of greater than 1 year. The eight largest studies included postmenopausal women over the age of 65 years. Eleven studies had comparable age and education status at baseline for the HRT and placebo groups, while four studies did not report education. The type of hormone therapy, dose, and mode of administration varied greatly across studies.

The effect of HRT on the development of mild cognitive impairment (MCI) was examined in two studies. MCI was defined by a strict protocol with four phases of ascertainment, including performance on neuropsychological tests and clinical assessment. Odds ratios (ORs) were calculated using fixed-effect models for rates of cognitive impairment, and weighted mean differences (WMDs) were calculated for continuous data. Meta-analyses showed no statistically significant effect of estrogen or estrogen plus progestin on prevention of MCI (OR for MCI with estrogen after 5 years 1.34 [95 percent CI 0.95 to 1.9]; OR for MCI with estrogen plus progestin after 4 years 1.05 [95 percent CI 0.72 to 1.54]). Estrogen or estrogen plus progestin treatment did not maintain or improve cognitive function (estrogen WMD -0.45 [95 percent CI -0.99 to 0.09]; estrogen plus progestin WMD -0.16 [95 percent CI -0.58 to 0.26]). There was no significant statistical heterogeneity ($I^2 < 50$ percent) in any of the analyses. No assessment of publication bias was performed.

The effect of HRT on various cognitive domains was also examined. In one study, the immediate Paired Associate test, a test of verbal memory, showed a significant beneficial effect after 2 to 3 months of estrogen therapy, but other larger studies found that 4 to 5 years of HRT was associated with impaired verbal memory using the CVLT (total WMD -0.52 [95 percent CI -0.91 to -0.13]; short delay WMD -0.24 [95 percent CI -0.44 to -0.04]; and long delay WMD -0.23 [95 percent CI] -0.43 to -0.03). Removal of two studies with inadequate allocation concealment also resulted in a loss of statistical significance in the Paired Associate test. In most studies, HRT had no effect on visual memory, but women randomized to receive CEE plus MPA in a large study showed a small, but statistically significant benefit on the Benton Visual Retention Test (BVRT), a test of short-term figural memory and visuo-constructional abilities (a difference of -0.27 [95 percent CI -0.49 to -0.05] errors per year). The clinical significance of this small change is unknown. There was no evidence for benefit in verbal fluency, word list recall, Wechsler Memory scale tests, Boston Naming, or PMA Vocabulary.

The review authors concluded that estrogen and combined estrogen plus progestin do not prevent cognitive decline in older postmenopausal women. Treatment with CEE plus MPA was associated with a small decrement in a number of verbal memory tests and a slight increase in figural memory. It is unknown whether HRT may benefit specific subgroups, such as younger women, women with different types of menopause (natural versus surgical), formulation, dose, or method of administration of HRT.

We identified one RCT examining the effect of raloxifene, a selective estrogen receptor modulator (SERM), on cognitive change.[39] This U.S.-based, double-blind, randomized, two-site, parallel-group, placebo-controlled study compared two doses of raloxifene (60 or 120 mg/day) to placebo on a battery of cognitive tests. One hundred and forty-three (143) postmenopausal women ranging in age from 45 to 75 years participated. Tests were derived from the Memory Assessment Clinics (MAC) computerized psychometric battery and the Walter Reed Performance Assessment Battery and were performed at baseline and at 1, 6, and 12 months. Study duration was 12 months. There were no differences in any cognitive measure following 1 year treatment with 60 or 120 mg raloxifene.[39]

Tierney et al. performed a 2-year randomized, double-blind, placebo-controlled trial of the effect of 1 mg 17-beta-estradiol and 0.35 mg norethindrone in 142 women between the ages of 61 and 87.[412] The primary outcome was short-delay verbal recall on the CVLT, and subjects were stratified by baseline performance on short-delay recall trial of the Rey Auditory Verbal Learning Test (RVLT). Women who scored at or above average on baseline RVLT showed significantly less decline on CVLT at 1 ($p = 0.007$) and 2 years ($p = 0.01$) than women who received placebo. There was no treatment effect in women who scored below average on RVLT at either year, suggesting that any benefit of estrogen on cognitive function may be limited to women with average or above average memory at baseline.

We also identified one good quality systematic review that examined the effect of dehydroepiandosterone (DHEA) supplementation on cognitive function.[36] Studies were included if subjects received DHEA or DHEA sulfate for any duration and were assessed by a valid neuropsychometric measure. The review included six studies; three from the United States and three from European countries (264 women and 281 men). Four studies included cognitive measures, while two had quality-of-life measures without cognitive testing. The age range of subjects was 44 to 85 years, and the duration for studies with cognitive measures ranged from 2 weeks to 1 year. Bias was assessed and described. DHEA 50 mg or placebo was administered daily, and outcomes were change in neuropsychometric test results.

No consistent benefit of DHEA supplementation on cognitive function was identified. The authors concluded that although the evidence is limited, controlled trials do not support a beneficial effect of DHEA supplementation on cognitive function in non-demented middle-aged or elderly people.

We identified one additional eligible United States-based study of DHEA on cognitive function involving administration of 50 mg DHEA to 225 cognitively normal subjects (aged 55 to 85 years) for 1 year.[413] This double-blind RCT measured cognitive function at baseline and 12 months using a battery of tests including the 3MS, word list memory and recall, Trail Making Part B, category fluency, and modified Boston Naming Test. The authors found no benefit in cognitive performance from treatment with DHEA.

The combined data do not support a benefit of 50 mg DHEA on cognition. No data are available on whether regular administration of DHEA has an effect on development of AD.

In summary, as described under Key Questions 1 and 2, respectively, some cohort studies of estrogen treatment suggest a decreased incidence of AD and, for symptomatic post-menopausal women, decreased cognitive decline. Double-blind, RCTs trials of estrogen, however, have not demonstrated a protective effect in preventing dementia or cognitive decline. Use of CEE plus MPA may increase the risk of dementia in postmenopausal women. In studies administering a battery of cognitive tests there is no consistent evidence for the benefit of routine administration of estrogen in any cognitive domain. Limited evidence suggests that there is also no beneficial effect of raloxifene, a SERM, or DHEA on cognitive function. There is insufficient evidence to determine whether other groups may benefit from estrogen treatment, such as women < 60 years of age; when to begin treatment; or whether effects differ in women who have natural versus surgical menopause. Other remaining questions about the effect of gonadal steroids on cognitive function include the type of estrogen or SERM used, whether it is supplemented with a progestin, the duration of therapy, and whether different modes of delivery would alter efficacy.

Cholinesterase inhibitors. We identified one good quality systematic review that examined the effects of cholinesterase inhibitors on the progression to dementia or AD and included as secondary outcomes, effects on cognitive testing.[44] The review included eight RCTs (4127

subjects). Four were multi-site studies in North America or the United States; one was a multi-site study in North America and Western Europe; one was a small, single-site U.S. study; and two did not report location. RCTs were selected that compared a cholinesterase inhibitor (donezpezil, galantamine, rivastigmine) to placebo control in participants with abnormal memory function and/or who met diagnostic criteria for mild cognitive impairment (MCI); individuals with dementia were excluded. Only English-language studies and studies presenting original data were included. Study quality was assessed using the Jadad criteria and was judged to be low to medium. Only one trial adequately described the randomization process; four followed an intention-to-treat principle for analysis; loss to followup was substantial and greater for intervention than control subjects; and in all but one study, multiple secondary outcome measures were evaluated without correction for multiple comparisons. Formal tests for publication bias (e.g., funnel plot) were not performed, but three completed studies[382-384] identified at ClinicalTrials.gov have not reported results, suggesting possible publication bias. One was a 16-week industry-sponsored study of rivastigmine that was terminated early in 2004.[384] The second was a 1-year National Institute of Mental Health (NIMH)-sponsored study of donepezil and gingko biloba extract completed in 2004.[383] Finally, the third was a 1-year, industry-sponsored study of donepezil in subjects with MCI completed in March 2007.[382] All three studies planned assessment of cognitive outcomes.

Of the eight identified trials, six (described in five publications[385-387,414,415]) reported effects on measures of cognition, activities of daily living, or neuropsychiatric symptoms. Cholinesterase inhibitors evaluated were donepezil 10 mg daily (two studies), rivastigmine 3 to 12 mg daily, and galantamine 16 or 24 mg daily (three studies). The number of subjects ranged from 19 to 1062. The two smaller studies followed subjects for ≤ 6 months, while the large studies followed subjects for 2 to 4 years. Participants were aged ≥ 50 years; race was reported in three studies (described in two publications[386,415]), and over 90 percent of subjects were white. A total of 36 different scales, tests, and neuropsychological batteries and two measures of volumetric imaging were used. The authors of the systematic review did not compute a summary estimate of effect due to important heterogeneity in the definition of MCI and the variability in outcome measures. Point estimates and 95 percent confidence intervals were reported for the 18 outcomes for which specific results from the original studies were reported. One small study[414] was excluded from analyses because results were only reported for 10 subjects and were not based on intention-to-treat analyses.

For the 18 outcomes reported, statistically significant differences favoring treatment were seen in individual studies only for the rate of brain volume atrophy by MRI (mean difference 0.21; 95 percent CI 0.14 to 0.27);[386] a measure of global cognition, the CDR-Sum of boxes (mean difference 0.2; 95 percent CI 0.0 to 0.4);[386] and the cognitive functions evaluated by the ADAS-Cog 13 (mean difference 1.9; 95 percent CI 0.5 to 3.3).[415] After correcting for multiple comparisons with Bonferroni methods, only the difference in rate of brain atrophy remained statistically significant. Treatment discontinuation due to adverse events was significantly higher for intervention subjects, ranging from 21 to 24 percent, compared to 7 to 13 percent in control subjects.

We identified two additional RCTs comparing 1 year of treatment with donepezil to placebo.[416,417] Doody and colleagues evaluated donepezil in subjects with amnestic MCI.[416] Amnestic MCI is of particular interest because it progresses to AD more commonly then general MCI. This U.S.-based, multi-center, industry sponsored study randomized 821 adults aged 45 to 90 to donepezil 5 mg daily for 6 weeks, then 10 mg daily for 42 weeks or placebo. Participants

were mostly male (54 percent), mostly white (87 percent), and had a memory complaint corroborated by an informant, along with neuropsychological testing consistent with amnestic MCI (see the evidence table in Appendix B for details). Individuals with medical conditions (e.g., neurological, psychiatric) that could affect cognition, who had taken a cholinesterase inhibitor for > 1 month, or who were taking a concomitant anticonvulsant, anti-Parkinsonian drug, stimulant, or drug with anticholinergic or procholinergic effects, were excluded. The followup rate (60.8 percent of those randomized) was low, with fewer subjects in the intervention group completing 48-week followup. The primary efficacy measures were the ADAS-Cog (range 0 to 70), a measure of cognition, and the CDR-SB (range 0 to 18), a measure of global function. Investigators pre-specified statistically significant differences on both measures to conclude treatment benefit. At 48 weeks, intervention subjects showed greater improvement from baseline than did control subjects on the ADAS-Cog (mean difference -0.9; SE 0.37; $p = 0.01$), but no significant difference on the CDR-SB (mean difference not given). Of eight secondary measures, donepezil-treated patients showed statistically significant benefit on two. More subjects assigned to donepezil (n = 72, 18.4 percent) than placebo (n = 32, 8.3 percent) discontinued treatment due to adverse effects.

Yesavage et al.[417] compared donepezil 5 mg daily for 6 weeks, and then 10 mg daily for 46 weeks, to placebo in 168 adults aged 55 to 90. At study weeks 13 and 14, all subjects received cognitive training consisting of 10 separate 2-hour sessions that taught visualization and mnemonic techniques. Participants were 65 years old on average, male (48 percent), in good general health, and had MCI (29 percent) or non-impaired cognitive functioning. Randomization and allocation concealment were adequate. Patients, providers, and outcome assessors were blind to intervention status, but followup rates were not reported. Analyses were conducted with random regression models using the intention-to-treat principle; funding was from the NIMH and VA.

For the primary cognitive outcomes (word list recall, name-face recall), there were no significant between-group differences at any of the three followup time points. Similarly, there were no significant between-group differences for secondary outcomes: symbol digit, digit span, quality of life, and functional status. More subjects treated with donepezil dropped out within the first 12 weeks (15 of 83 versus 6 of 85), or experienced muscle cramps (19 versus 1) or insomnia (18 versus 8; $p < 0.05$ for all comparisons).

In summary, a systematic review found six low- to medium-quality trials reporting the effects of cholinesterase inhibitors on cognition in subjects with MCI; three other studies have not reported outcomes. We identified two additional donepezil trials that did not show treatment benefit on the primary cognitive outcomes at 1 year, but did show greater dropouts with treatment. In aggregate, over 5000 subjects have participated in these trials, but no consistent positive effects have been demonstrated. Treatment discontinuations due to adverse effects are consistently higher in the cholinesterase inhibitor-treated groups.

Memantine. We did not identify any systematic reviews or primary studies that evaluated the effects of memantine on cognitive testing in subjects who were cognitively normal or had mild cognitive impairment.

Social, Economic, and Behavioral Factors

Social engagement. No good quality systematic reviews or RCTs were identified that evaluated a social engagement intervention to improve or maintain cognitive ability or function.

Cognitive engagement. Our review identified three reports from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial that examined the effects of cognitive training on improving long-term cognitive performance.[418-420] In the ACTIVE trial, participants were randomized to one of three cognitive treatment groups (memory training, reasoning training, or speed of processing training) or the control group with no contact. Participants in the treatment groups attended 10 sessions over a 5- to 6-week period. A randomly selected subsample of 60 percent of each treatment group received four sessions (over a 2- to 3-week period) of booster training at 11 months and then again at 35 months after the initial training sessions. Primary outcomes were performance on cognitive measures and functional performance in daily activities.

Individuals were recruited from senior housing, community centers, hospitals, and medical clinics in six cities in the United States. Participants had to be over age 65 years, living independently, and able to perform their activities of daily living (ADLs) independently. Excluded individuals had an MMSE score < 22 points; reported a diagnosis of AD; reported substantial functional decline; reported having a medical condition that could predispose them to severe functional decline or death; had severe loss of vision, hearing, or ability to communicate; had recently participated in another cognitive training study; or planned to move out of the area during the time course of the trial. A total of 2802 individuals were enrolled and appropriately randomized. Dependent variables were measured at baseline, immediately post-treatment, and then at 1, 2, and 5 years post-treatment. Eighty-nine percent of participants completed at least eight training sessions.

The mean age of the sample was 73.6 (5.9) years. Comparisons of baseline characteristics among intervention and control groups were reported. Followup rates were 80 percent at 2 years and 63 percent at 5 years. Although participants who did not complete all 5 years of data collection were more likely to be older, male, have less education and more health problems, and have lower cognitive function on baseline measures, there were no significant interactions between treatment group and these variables.

Each intervention group showed improvement in the targeted cognitive ability compared with baseline, and the effect was still evident at 2 years post-intervention (memory: effect size 0.17; $p < 0.001$; reasoning: effect size 0.26; $p < 0.001$; speed of processing: effect size 0.87; $p < 0.001$).[420] Booster training increased training gains in speed ($p = 0.001$) and reasoning ($p = 0.001$) interventions at both the 1-year and the 2-year followup. One of the outcome measures was an estimate of reliable change. At the 2-year followup, only the speed of processing training group showed marked differences in this outcome, with 79 percent of the booster speed processing group showing reliable change, compared to 65 percent of the no booster group and 37 percent of the control group. No training effects were observed on everyday functioning at the 2-year followup.

At the 5-year followup,[418] each intervention group maintained positive effects on its specific targeted cognitive ability (memory: effect size 0.23 [99 percent CI 0.11 to 0.35]; reasoning: effect size 0.26 [99 percent CI 0.17 to 0.35]; speed of processing: effect size 0.76 [99 percent CI 0.62 to 0.90]). Booster training on the targeted ability produced additional improvement for reasoning performance (effect size 0.28; 99 percent CI 0.12 to 0.43) and for speed of processing

performance (effect size 0.85; 99 percent CI 0.61 to 1.09). The booster training for the speed of processing group, but not for the other two groups, showed a significant effect on the performance-based functional measure of everyday speed of processing (effect size 0.30; 99 percent CI 0.08 to0.52).

A third report on the ACTIVE trial[419] assessed whether a subgroup of individuals classified as memory impaired showed as much improvement on cognitive measures after training as the remainder of the group who were not memory impaired. Individuals scoring ≥ 1.5 standard deviations below their expected score on a verbal memory test at baseline were considered to be memory impaired (n = 193). Results indicated that memory-impaired participants failed to benefit from memory training, but did show normal training gains after reasoning (effect size 0.28; $p < 0.05$) and speed training (effect size -0.76; $p < 0.001$). The study authors concluded that memory function mediates the response to some forms of cognitive training.

Our search did not identify any additional trials. In summary, one large cognitive training trial has shown modest long-term benefits from cognitive training over a 5- to 6-week period with subsequent periodic booster training. Overall, the smallest effect is shown on the tasks of verbal declarative memory.

Physical activities. We identified one good quality systematic review examining the association of physical activity interventions on cognitive change over time.[48] This review identified 11 eligible RCTs with participants that met the following criteria: aged 55 or older, not demented due to any reason, not recovering from surgery, and did not have comorbidities that precluded them from participation in physical exercise programs. Acceptable physical activity interventions were any form of exercise of any intensity, duration, or frequency that was aimed at improving cardiorespiratory fitness. The studies identified in this review had a followup period of no greater than 6 months, and the majority lasted 4 months or less. There were no studies identified examining the longer term effects of physical activity on cognition.

The authors of the review reported that 8 of the 11 eligible studies showed an improvement in at least one aspect of cognitive function, but the domains of cognitive function that improved were not the same in each study, and the majority of comparisons yielded no significant results. Thus, the review authors concluded that there were insufficient data to state that aerobic physical activity improves cognitive function.

Our own review identified one eligible RCT that examined the effect of physical activity on improving or maintaining long-term cognitive performance.[421] Participants were randomized to an education and usual care group or to a 24-week home-based program of physical activity. The primary outcome was change in the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores over 18 months. Individuals were recruited from a number of sources, including two memory clinics and the general community, using advertisements in the local media in Perth, Australia. Participants had to be over age 50 years and had to have responded "yes" to the question, "Do you have any difficulty with your memory?" Individuals excluded had scores lower than 19 of 50 on the TICS-m (a score consistent with significant cognitive impairment or dementia); had a Geriatric Depression Scale-15 score of 6 or higher; reported drinking more than four standard units of alcohol a day; had a chronic mental illness, such as schizophrenia; had medical conditions likely to compromise survival, such as metastatic cancer, or render them unable to do in physical activity, such as severe cardiac failure; or had severe sensory impairment or lack of fluency in written or spoken English. Additional exclusion criteria were a diagnosis of dementia, an MMSE score < 24, a Clinical Dementia Rating ≥ 1, and inability to walk for 6 minutes without assistance.

The aim of the physical activity intervention was to have participants engage in moderate intensity physical activity for at least 150 minutes per week, to be completed in three 50-minute sessions. Participants recorded the details of their physical activities in a diary. To enhance compliance with the program, participants were also given a modified behavioral intervention package based on social cognitive theory. Participants in the usual care control group received educational material about memory loss, stress management, healthful diet, alcohol consumption, and smoking, but not about physical activity. Participants in the physical activity group were also offered these educational materials.

A total of 170 individuals were enrolled and appropriately randomized. Outcomes were measured at baseline, and then at 6, 12, and 18 months after baseline. A total of 81.2 percent of the participants completed the trial. Adherence to the prescribed physical activity for the 24 weeks was 78.2 percent. The mean age of the sample was 68.6 (8.7) for the exercise group and 68.7 (8.5) for the control group. Baseline characteristics were reported for the intervention and control groups, but statistical comparisons were not reported. The values reported in Table 1 of the manuscript suggest that the control group may have had higher frequency of moderately intense physical activity at baseline, but without a statistical comparison that cannot be confirmed. Women were more likely than men to drop out in both groups, and those who dropped out had higher ADAS-Cog scores than those who remained in the trial.

At the 6-month point, the physical activity group showed a decline of -0.26 (95 percent CI -0.89 to 0.54) points on the ADAS-Cog (lower scores indicate better performance), and the control group showed an increase of 1.04 (0.32 to 1.82) points on this measure. At the 18-month followup, the difference between the two groups had diminished, with the treatment group showing a decline on the ADAS-Cog of -0.73 (-1.27 to 0.03) points, and the control group showing a decrease of -0.04 (-0.46 to 0.88). The repeated measures ANCOVA across the 6-, 12-, and 18-month followups showed statistically significant less decline in the intervention group ($p = 0.04$). Analyses on secondary outcomes showed differences on the delayed word list task, with the physical activity group showing an increase of 0.45 (0.03 to 0.87) points compared to the control groups increase of 0.38 (-0.01 to 0.77) points at the 6-month followup. This pattern of differences continued at the 18-month followup, with the physical activity group showing an increase of 0.76 (0.41 to 1.10) points, and the control group showing a decrease of -0.02 (-0.36 to 0.32) points ($p = 0.02$ for ANCOVA for repeated measures across the three time points). There were no statistically significant differences on the other cognitive measures. Similar differences were seen on the ADAS-Cog when the analyses were limited to individuals categorized as having mild cognitive impairment. When considering only those individuals who completed all assessments, the physical activity group showed more improvement or maintenance of cognition on the ADAS-Cog ($p = 0.009$ for ANCOVA for repeated measures across the three time points), the delayed word list ($p = 0.01$), and the Clinical Dementia Rating scale (CDR) ($p = 0.003$).

In summary, this RCT found a modest, but positive effect of physical activity on one relatively comprehensive cognitive measure (ADAS-Cog) and also on a delayed recall task over an 18-month period, that is, 1 year post-intervention. The participants were individuals who confirmed having problems with their memory, and in fact some met criteria for a diagnosis of mild cognitive impairment, suggesting that the individuals were likely at increased risk for cognitive decline. Thus, relatively greater preservation of cognition associated with physical activity in this group may be particularly meaningful. Furthermore, the study authors noted that the effect associated with physical activity was comparable to or better than the results from some of the medication treatment trials.

Other leisure activities. We did not identify any good quality systematic reviews or RCTs that assessed the effects of non-cognitive, non-physical leisure activities for preserving cognitive ability.

Nicotine. We did not identify any good quality systematic reviews or RCTs that evaluated the effects nicotine for preserving cognitive ability.

Key Question 5 – Relationships Between Factors Affecting Alzheimer's Disease and Cognitive Decline

Key Question 5 is: What are the relationships between the factors that affect Alzheimer's disease and the factors that affect cognitive decline?

Introduction

Concordance for factors affecting cognitive decline and Alzheimer's disease has a number of potential implications. A consistent body of evidence increases our confidence in the observed association. It is also consistent with the proposed analytic framework that the symptoms of AD begin with insidious cognitive decline that progress to more marked cognitive and functional impairment. Finding consistent evidence for cognitive decline and AD would reinforce the potential effectiveness of early interventions that could diminish both the risk of cognitive decline and AD. Discordant findings weaken our confidence in the association, but may simply reflect the heterogeneity of the etiology of cognitive decline; that is, cognitive decline may be due to normal aging mechanisms or the prodromal stage of other types of dementing disorders such as vascular or frontal lobe dementia. To address this question, we used the results from Key Questions 1 through 4 to compare the evidence for the effects of each exposure on risk of AD and cognitive decline. For factors with both randomized controlled trial (RCT) and observational evidence, we first compared the consistency of findings across study designs for each outcome. RCTs are a stronger design than observational studies and were prioritized when there were high-quality studies that used robust outcome measures. When studies showed a consistent effect on risk that was in the same direction for both AD and cognitive decline, we judged the results concordant. For many factors, the available data are quite limited, and concordant evidence across outcomes should not necessarily be interpreted as a robust finding.

Nutritional and Dietary Factors

These factors include vitamins, diet composition, and gingko biloba. In Table 70 we summarize the number of studies and subjects and provide a qualitative summary of the association.

Concordant evidence. Concordant evidence for these factors was as follows:

- Increased risk with higher exposure: None.
- No consistent association with risk: Beta carotene, flavonoids, gingko biloba, multivitamins, vitamin B12, vitamin C, and vitamin E.
- Decreased risk with higher exposure: Mediterranean diet (limited evidence).

Discordant evidence. In observational studies, folic acid was associated with decreased risk for AD, but this association was not consistent for cognitive decline. RCTs did not show a protective effect for folic acid. In observational studies, omega-3 fatty acids were associated with less risk for cognitive decline but not a decreased risk for AD. No RCTs of at least a year's duration have been conducted for omega-3 fatty acids.

Concordance not determined. For some factors, concordance was not determined because of the lack of evidence for both AD and cognitive decline, namely: diet composition, trace metals, vitamin B3 (niacin), and vitamin B6 (pyridoxine). For fruit and vegetable consumption, we made the judgment that the exposures were not comparable across outcomes and concordance could not be determined. Preliminary evidence suggests that saturated fat intake may be associated with AD and cognitive decline, but the evidence was considered too limited to judge concordance.

Table 70. Summary of evidence for association between nutritional factors and AD or cognitive decline

Exposure	B vitamins		Vitamins C and E, beta-carotene		Gingko biloba		Omega-3 fatty acids		Mediterranean diet	
Design	**Cohort**	**RCT**	**Cohort**	**RCT**	**Cohort**	**RCT**	**Cohort**	**RCT**	**Cohort**	**RCT**
Studies (subjects)	5 (5927)	None	12 (19,874)	1 (769)	None	1 (3069)	9 (24,980)	None	2 (> 3000)	None
Association with AD*	Folic acid: Decreased risk B12: No consistent association	-	No consistent association	Vitamin E: No association	-	No association	No consistent association	-	Possibly decreased risk	-
Studies (subjects)	5 (5927)	2 (2440)	8 (11,033)	Vitamin E: 4 (10,473) Multi-vitamin: 1 (910)	-	1 (134)	5 (12,392)	1 (302)	2 (3285)	None
Association with cognitive decline*	Folic acid, B6, B12, niacin: No consistent association	Folic acid, B6, B12: No consistent association	No association	Vitamin E and multi-vitamin: No association	-	No association	Possibly decreased risk	No association	Decreased risk	-
Concordance/ discordance for AD and cognitive decline outcomes	B12: Concordant for no association Folic acid: Discordant B6 and niacin: Both outcomes not studied		Concordant for no association, but limited evidence for beta-carotene, flavonoids and multivitamins		Concordant for no association, but limited evidence		Discordant. Exposure definitions variable; duration of RCT only 6 months		Concordant for decreased risk, but limited evidence	

Abbreviations: AD = Alzheimer's disease; RCT = randomized controlled trial
*Direction of risk for higher exposure (intake) and AD or cognitive decline.

Medical Factors

Vascular, other medical, and psychological and emotional health. These factors include diabetes mellitus, metabolic syndrome, hypertension, hyperlipidemia, homocysteine, sleep apnea, obesity, traumatic brain injury, and depressive and anxiety disorders. In Table 71 we summarize the number of studies and subjects and provide a qualitative summary of the association.

Concordant evidence. Concordant evidence for these factors was as follows:

- Increased risk with higher exposure: Diabetes mellitus, depressive disorders (although evidence less consistent for cognitive decline).
- No consistent association with risk: Hypertension, homocysteine, obesity.

Discordant evidence. In observational studies, metabolic syndrome was associated with increased risk for cognitive decline in the young-old, but was not associated with risk for AD. Hyperlipidemia was associated with AD in mid- but not late-life and did not show a consistent association with cognitive decline.

Concordance not determined. For some factors, concordance was not determined because of the lack of evidence for both AD and cognitive decline, namely: anxiety disorders and traumatic brain injury. There were no studies for sleep apnea or resiliency.

Table 71. Summary of evidence for association between medical factors and AD or cognitive decline

Exposure	Diabetes mellitus	Metabolic syndrome	Hyperlipidemia	Homocysteine	Hypertension	Obesity	Depression
Studies (subjects)	13 (> 100,000)	2 (5603)	8 (14,331)	4 (2662)	11 (18,793)	7 (21,577)	16 (100,065)
Association with AD*	Increased	No	Midlife: Increased Late-life: No	No	No consistent association	No association	Yes
Studies (subjects)	12 (47,629)	4 (5713)	5 (20,184)	5 (3409)	19 (>43,000)	3 (8475)	13 (32,969)
Association with cognitive decline*	Possibly increased risk	Increased risk, except for age > 85 years	No consistent association	No consistent association	MCI: No association Global: No association Processing speed: No consistent association	No consistent association	Probably increased risk
Concordance/ discordance for AD and cognitive decline outcomes	Concordant, increased risk	Discordant but limited evidence	Discordant	Concordant, but heterogeneity in how exposure defined	Concordant, no association Heterogeneous studies	Concordant, no association	Concordant, increased risk

Abbreviations: AD = Alzheimer's disease; MCI = mild cognitive impairment
*Direction of risk for higher exposure and AD or cognitive decline.

Prescription and non-prescription medications. These factors include HMG-CoA reductase inhibitors (statins), antihypertension medications, non-steroidal anti-inflammatory medications (NSAIDs), gonadal steroids (estrogens, raloxifene, dehydroepiandosterone), and cholinesterase inhibitors. In Table 72 we summarize the number of studies and subjects and a qualitative summary of the association.

Concordant evidence. Concordant evidence for these factors was as follows:

- Increased risk with higher exposure: None
- No consistent association with risk or rate of cognitive decline: Cholinesterase inhibitors, estrogens

Discordant evidence. Observational studies suggest that statins decrease risk for AD, but observational and trial data do not show a consistent benefit for cognitive decline. Treatment with antihypertensive medication may decrease risk for AD, but no protective effect was found for cognitive decline. These studies are limited by the absence of trial data for AD, and by data from a trial for cognitive decline that used an outcome measure that is relatively insensitive to change. In observational studies, exposure to NSAIDs were possibly associated with decreased risk for AD and cognitive decline, but RCTs support an increased risk for AD and no consistent association for cognitive decline.

Concordance not determined. For some factors, concordance was not determined because of the lack of evidence for both AD and cognitive decline, namely: raloxifene and dehydroepiandosterone. There were no studies for memantine.

Table 72. Summary of evidence for association between medications and AD or cognitive decline

Exposure	HMG-CoA reductase inhibitors (statins)		Anti-hypertensive medication		NSAIDs		Gonadal steroids		Cholinesterase inhibitors	
Design	**Cohort**	**RCT**	**Cohort**	**RCT**	**Cohort**	**RCT**	**Cohort**	**RCT**	**Cohort**	**RCT**
Studies (subjects)	6 (17,840)	None	8 (19,7373)	5 (20,563)	8 (24,275)	2 (3985)	2 (1596)	2 (7479)	0	8 (4127)
Association with AD*	Decreased risk		Probably decreased risk	No association for dementia (not specifically AD)	No consistent association	Increased risk	Decreased risk	CEE: No association CEE + MPA: Increased risk	-	No
Studies (subjects)	4 (6827)	2 (26,340)	2 (3599)	4 (14,107)	6 (33,600)	3 (8972)	9 (16,294)	CEE: 18 (10,256) Raloxifene: 1 (143) DHEA: 7 (770)	0	10 (5116)
Association with cognitive decline*	Inconsistent association	No association	No association	Inconsistent association	No association; Possibly decreased risk in some subgroups	Aspirin: No association Naproxen: Increased risk Celecoxib: No association	No association, except decreased risk in sympto-matic post-menopausal women	CEE: No association Raloxifene: No association DHEA: No association	-	No association

Exposure	HMG-CoA reductase inhibitors (statins)		Anti-hypertensive medication		NSAIDs		Gonadal steroids		Cholinesterase inhibitors	
Design	**Cohort**	**RCT**	**Cohort**	**RCT**	**Cohort**	**RCT**	**Cohort**	**RCT**	**Cohort**	**RCT**
Concordance/ discordance for AD and cognitive decline outcomes	Discordant		Discordant. General dementia but not AD evaluated in RCTs		Concordant across outcomes but inconsistent across study designs		CEE: Concordant for no association DHEA, raloxifen, CEE + MPA: Both outcomes not studied			Concordant for no association. Possible publication bias

Abbreviations: AD = Alzheimer's disease; CEE = conjugated equine estrogen; DHEA = dehydroepiandosterone; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; MPA = medroxyprogesterone; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial
*Direction of risk for higher exposure (intake) and AD or cognitive decline

Social, Economic, and Behavioral Factors

These factors include early childhood factors, education and occupation, social engagement, cognitive engagement, physical activities, other leisure activities, smoking, and alcohol use. In Table 73 we summarize the number of studies and subjects and a qualitative summary of the association.

Concordant evidence. Concordant evidence for these factors was as follows:

- Increased risk with higher exposure: tobacco.
- No consistent association with risk of AD or rate of cognitive decline: early childhood socioeconomic environment (limited data).
- Decreased risk with higher exposure:
    - Observational studies show that greater cognitive engagement (imprecise measures of exposure) decrease risk of AD and cognitive decline. Observational studies are limited by imprecise and variable measures of exposure; the effect of cognitive training on cognitive decline has been evaluated in a single RCT.
    - Greater physical activity in late adult life is associated with decreased risk of AD and less cognitive decline, but conclusions are limited by imprecise measures of exposure, variable measures of cognitive decline, and a single small RCT.

Discordant evidence. Light to moderate alcohol intake is associated with a decreased risk of AD, and lower educational level is associated with an increased risk of AD; neither shows a consistent association with cognitive decline.

Concordance not determined. For some factors, concordance was not determined because of the lack of evidence for both AD and cognitive decline, namely: physical activity during mid-adult life. For marital status, data are insufficient to determine concordance. Occupation exposure, social support, and social network were defined too heterogeneously both within and between the studies for AD and cognitive decline to determine concordance. Other leisure activities are not consistently associated with AD but probably decrease the risk of cognitive decline; again, definition of exposure varied substantially between studies, leading us to conclude that the evidence is insufficient to determine concordance.

Table 73. Summary of evidence for association between social/economic/behavioral factors and AD or cognitive decline

Exposure	Childhood exposures	Education/ occupation	Social engagement	Other leisure activities	Alcohol	Tobacco	Physical activity in late adults		Cognitive engagement	
Design	**Cohort**	**Cohort**	**Cohort**	**Cohort**	**Cohort**	**Cohort**	**Cohort**	**RCT**	**Cohort**	**RCT**
Studies (subjects)	1 (859)	Education: 11 (25196) Occupation: 5 (6029)	Marital status: 3 (6699) Social network: 1 (1473) Social support: 2 (4365)	2 (7464)	6 (14,646)	12 (21,718)	12 (25,603)	None	4 (7723)	None
Association with AD*	No association	Education: Decreased risk Occupation: No	Never married: Increased risk Less social network: Increased risk Less social support: Increased risk	Inconsistent association	Decreased risk	Increased risk	Probably decreased risk	-	Decreased risk	-
Studies (subjects)	3 (6,861)	Education: 14 (43201) Occupation: 4 (7277)	Marital status/ cohabitation: 7 (16565) Social network: 5 (10926) Social support: 5 (15459)	3 (9599)	7 (15,581)	14 (33685)	8 (17351)	1 (170)	4 (6285)	1 (2802)
Association with cognitive decline*	No association	Education: Inconsistent association Occupation: Possibly	Marital status: Inconsistent association Social network: Inconsistent	Probably decreased risk	No association	Increased risk	Probably decreased risk	Decreased risk	Probably decreased risk	Slightly decreased risk

Exposure	Childhood exposures	Education/ occupation	Social engagement	Other leisure activities	Alcohol	Tobacco	Physical activity in late adults		Cognitive engagement	
Design	**Cohort**	**Cohort**	**Cohort**	**Cohort**	**Cohort**	**Cohort**	**Cohort**	**RCT**	**Cohort**	**RCT**
		decreased risk	association Social support: Inconsistent association							
Concordance/ discordance for AD and cognitive decline outcomes	Concordant for no association Exposure measure variable.	Education: Discordant Occupation: Evidence inadequate to determine	Evidence inadequate to determine	Evidence inadequate to determine	Discordant	Concordant for increased risk	Concordant for decreased risk but exposure measures variable and imprecise; little trial data; cognitive decline measured variably		Concordant for decreased risk but exposure measures imprecise and variable; little trial data	

Abbreviations: AD = Alzheimer's disease; RCT = randomized controlled trial

*Direction of risk for higher exposure (intake) and AD or cognitive decline.

Toxic Environmental Exposures

For toxic environmental exposures, concordance was not determined because of the lack of evidence for both AD and cognitive decline.

Genetic Factors

Of the six genes associated with risk for AD and included in this review, only one (APOE 4) has been evaluated in cohort studies for risk of cognitive decline. These studies are generally concordant. The presence of APOE e4 increases the risk of AD and the risk of cognitive decline, especially on some memory tasks and tasks of perceptual speed.

Key Question 6 – Future Research Needs

Key Question 6 is: If recommendations for interventions cannot be made currently, what studies need to be done that could provide the quality and strength of evidence necessary to make such recommendations to individuals?

Introduction

To address this question, we first identified the factors included in the present review that are potential interventions. Only a subset of the factors considered meets this criterion. Childhood exposures, education, genetics, toxic exposures, and the medical conditions considered are not potential interventions, but rather potential targets for intervention. Components or intermediary measures of some of the risk factors evaluated (e.g., treatment for diabetes mellitus) may be appropriate for intervention, but these factors were not on the list of exposures to be considered in this review. This discussion focuses primarily on the factors reviewed that are potential interventions.

Based on a review of the quality, strength, consistency, and extent of evidence for each factor, for AD, the only risk factors with moderate quality evidence for increased risk of AD were the APOE e4 allele, some non-steroidal anti-inflammatory drugs (NSAIDs), and conjugated equine estrogen with methyl progesterone. For cognitive decline, there was moderate quality evidence for an increased risk with some NSAIDs, and high quality evidence for a decreased risk with cognitive training. Chapter 5 describes the other factors that had low quality evidence supporting either an increased or decreased risk of AD or cognitive decline.

Given the number of studies that have investigated one or more of the factors on this lengthy list of putative risk or protective exposures for AD and cognitive decline, this much abbreviated list of factors with even moderate support may seem discouraging. But it is important to note that the factors on the list that lack even moderate supporting evidence may be associated with cognitive decline and AD; there just was not sufficient evidence to draw such a conclusion. For example, findings from cohort studies showed an association between statins and decreased AD risk, but there were no RCTs confirming this finding. The findings on the Mediterranean diet and other dietary components, such as folic acid, look intriguing, but the research is limited or too heterogeneous to draw firm conclusions. Many of these prior studies, including those reporting

on factors with some supporting evidence, should be viewed as exploratory investigations that need to be followed up by well-designed hypothesis-testing observational studies or RCTs. The current literature does not provide adequate evidence to make recommendations for interventions.

We discuss below the characteristics unique to AD that present particular challenges when assessing the effect of given exposures on disease outcome. We also discuss some of the disease-related issues and the methodological challenges to assimilating the present studies in this area.

Protracted Course of Disease without Overt Clinical Symptoms

Issues. Neuropathological evidence suggests the pathological changes associated with AD may begin as early as the 4th decade of life, but overt clinical symptoms do not present until years later during the 7h, 8th, and 9th decades of life.[20] Subtle cognitive changes may begin prior to age 60 among those with an APOE e4 allele,[422] but these changes are difficult to detect in individuals. The age criteria for the present review was age 50 and older, but the majority of studies examined exposures well beyond mid-adult life, meaning that for some individuals (e.g., APOE e4 allele positive individuals) or factors the studies may have missed the critical exposure time period. The extended sub-clinical prodromal phase of AD also means that exposures measured 1 to 2 years prior to onset of symptoms may conflate the risk factor exposure with prodromal AD.

Addressing the gap. Observational studies need to assess exposures initially years prior to expected onset of symptoms. The collection of exposure data should continue over an extended period of time because it is not known whether exposures with a protective effect or those with a detrimental effect may still be influential even after the pathological process has begun. It is also important to collect longitudinal exposure data to examine whether the timing of the exposure makes a difference, and whether changes in exposure over time alter risk of cognitive decline. Prospectively collecting this exposure information for decades prior to onset of clinical disease is costly and logistically challenging. Realistically, intermediate or shorter-term outcomes may need to be integrated into such a life course approach to make the studies viable. Some of the initial work in this area may be able to use established registries. In fact, some research groups have already taken advantage of longitudinal registry databases, such as those from the Veteran's Administration and health maintenance organizations, to collect more objective information on exposure variables that spans decades. The value of these registries can be optimized by linking the exposure data to a prospective and comprehensive evaluation for diagnosis of dementia. Multiple registries could contribute data to establish research consortia to conduct planned prospective meta-analysis. This would be particularly useful for some of the research questions that require very large sample sizes such as assessing interaction effects and differential effects in sample subgroups. This approach would have the potential additional benefit of encouraging some standardization of data collection methods and instruments across studies.

The protracted course of the disease also means that early symptoms of AD may be mistakenly reported as risk factors for the disease when in fact they are correlates or symptoms of disease. An example of this is depression, which is often a symptom of AD, especially in the early stages of disease. It is difficult to separate depressive symptoms that are antecedents of AD from depression that is an early symptom of the disease.

The long prodromal phase of AD means that interventions should not only be implemented as early as possible, but also that there also may be windows of time during which interventions

are most effective, and these time periods may differ for different risk factors and interventions. Due to the long prodromal period of AD, RCTs also need to continue for extended periods of time. The current review identified few clinical trials that were even 1 year in length. If exposures throughout the lifespan are being examined for their role in AD and cognitive decline in late life, it is unrealistic to expect interventions of less than 1 year to change the path of the disease. However, if unaffected or mildly affected individuals are to be exposed to interventions for long periods of time, the interventions need to be low risk. For example, one intervention trial of non-steroidal anti-inflammatory (NSAID) medication (the Alzheimer's Disease Anti-inflammatory Prevention Trial [ADAPT]) was discontinued due to concerns about serious side-effects of the medication.[379] It is important to note that the interventions do not need to be pharmacologic; low-risk interventions could involve lifestyle interventions like exercise and diet, or aggressively monitored treatment of existing diseases like diabetes, cholesterol, or hypertension. Another approach to limiting the period of exposure to an intervention and to optimize outcome would be to enrich the sample with individuals at particularly high risk of progressing to AD. This would result in shorter followup time and smaller sample sizes required to evaluate the intervention. Some RCTs have already used this approach.[372] Another efficient way to test interventions for potential risk factors such as diabetes mellitus is to design robust measures for cognition as a secondary outcome in trials designed to test multifactorial interventions for the disease of interest. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) and ACCORD-MIND (Action to Control Cardiovascular Risk in Diabetes – Memory in Diabetes) trials are current examples of this strategy.[423,424]

Although long-term RCTs are the ideal approach, in many cases the barriers to implementing such studies may make them unrealistic. In these cases, alternative analytical approaches such as structural equation modeling, path analysis, and multi-level modeling applied to life course data may help to identify causal relations between exposure and disease.[425] In addition, alternative designs such as randomized encouragement designs and non-random quantitative assignment of treatment designs are options which may be more feasible and still allow one to make causal inferences.[426]

Long-term studies may not only be unrealistic but they also create their own issues, such as attrition due to numerous reasons (e.g., mortality, refusal), which need to be carefully considered in the planning stages. Those who continue to participate throughout the course of the study may be younger, healthier, and of higher socioeconomic status than those who discontinue participation.[427] This may create selectivity in the sample over time, another issue that should be addressed in the planning stages of the study. Although evidence-based approaches to decrease attrition are not well established, a recent systematic review found that studies using multiple strategies such as community involvement, frequently updating participant contact information, financial incentives, and minimizing participant burden were associated with less attrition.[428]

Lack of Validation of Exposure Measures

Issues. There are a number of issues regarding the measurement of exposures. Large cohort studies often rely on self-reported information from questionnaires that briefly assess a range of exposures. Typically any given exposure is assessed with just a few questions. Often responses to questions are then combined post hoc to create exposure variables that were never intended when the questionnaire was designed. Often the derived exposure variables have not been formally assessed for construct validity; that is, do the variables measure what they say they do?

For example, among the studies cited in this review, there was a good deal of overlap among the activities categorized as cognitive, physical, and leisure. Validation for the categorization was not provided. Another example that raised questions about construct validity was that some studies interpreted exposure on a single item to have broader meaning. For example, the variable "being married" was used to indicate more social support, even though the benefits of marriage are multi-dimensional. Another issue related to construct validity is that exposure variables may actually serve as surrogates for other variables. An example of this is that education may be a surrogate for premorbid intellect or cumulative advantage throughout life. The association between a greater number of years of education and lower risk of AD may also reflect an insensitivity of diagnostic methods to identify impairment among those with high education. Identifying an association between a surrogate factor and disease outcome is an important first step, but prior to implementing RCTs or interventions based on these findings, the underlying risk factor needs to be identified.

Another issue is the imprecision of the measurement of exposure in observational studies. One example of this would be the accuracy of self-report information on food intake and the conversion of this information to actual nutritional components. In addition, it is unclear whether intake of nutrient directly equates to in-vivo level of nutrient. The studies reporting validation analyses indicate a limited correlation between responses on the food frequency questionnaire and 24-hour records of food intake. Another example of imprecise exposure data is the variability in the type, duration, and frequency of exercise. It is difficult to retrospectively assess exercise activity over decades of exposure when there may be periods of regular activity followed by no activity.

Yet another issue of measurement is that studies ordinarily investigate a single exposure, but many of the exposures of interest are likely inter-related. This is particularly true for nutrition, as it is unrealistic to consider single nutrients in isolation. In addition, many of the exposures of interest are behaviors that commonly co-occur in individuals aiming to maintain a healthy lifestyle; measuring any single exposure among the numerous healthy behaviors would lead to inaccurate conclusions.

Another issue relates to how exposure is defined. It was often not clear whether exposure levels were determined a priori and whether they were linked to biological rationale, clinical relevance, or informed by prior studies. For example, definitions of hypertension and nutritional intake levels varied across studies or were defined by proportions of the available data. In addition, categorizing the exposure based on distributional properties (e.g., quartiles) may decrease the power to detect an association. To assist in interpreting the results, the reader will need to know whether the analysis was exploratory, with multiple definitions of exposures being tested, or whether the analysis addressed a specific hypothesis, with the exposure level being predetermined as part of the hypothesis.

One final issue that is related to both exposure and outcome is that power analyses were rarely reported in the included studies. Providing a priori power analyses for planned analyses or post hoc calculations for exploratory analyses would allow readers and systematic reviewers to better understand if null findings were due to low power.

Addressing the gap. There are multiple issues related to exposure variables, as noted above. A few basic steps would advance the field substantially in addressing these issues, but some of these steps are quite challenging. A first step should be developing standard methods to measure exposure and provide validation data to show that the measure is reliable and valid. Some areas of research have established "measures warehouses" to standardize the measurement with the

aim of advancing the research. Similar to the idea of a measures warehouse, sponsors of research might establish a web-based resource for dementia studies that inventories exposure measures and data about validity. Finally, editors for more journals might require that authors follow standard guidelines for reporting observational studies (e.g., the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] guidelines).[429]

Sensitivity, Validation, and Homogeneity of Outcome Measures

Issues. For inclusion in this review, we required that studies on AD used standard diagnostic criteria. However, there was wide variation in how these diagnostic criteria were operationalized, particularly regarding the extent of neuropsychological testing used and whether information was collected from both a knowledgeable informant and the study participant to determine the diagnosis. In contrast to AD, for mild impairment the diagnostic standards are still evolving, with most diagnostic nomenclature suggesting that cognitive decline leading to mild impairment appears to have many causes. For example, there are multiple types of mild cognitive impairment (MCI) and cognitive impairment not demented (CIND). This heterogeneity in both the cognitive profile and most likely the underlying etiology may be part of the reason why only a few cognitive measures show significant change associated with a risk factor. This alone makes interpretation of the results difficult. But compounding the issue are the facts that different cognitive measures are used across studies, and associations between specific exposures and specific cognitive tests or tests in the same cognitive domain are not replicated across studies. The heterogeneity of cognitive measures has made synthesis of the literature on cognitive decline difficult.

Often studies reported that exposure to a factor was associated with statistically significant, but very modest decline on one or two cognitive measures only. It is important to note that statistical significance does not equate to clinical significance.

Addressing the gap. Further work is required to reach a consensus on which cognitive measures are the best validated, most responsive to change, and measure the needed domains. If the experts could agree on a limited battery of measures, it would make synthesis of the literature more straightforward and allow for pre-planned meta-analysis. If the same exposure and cognitive assessments were used in different studies, then datasets could be combined and patient level meta-analysis could be performed. This is an efficient way to look at subgroups rather than powering individual studies for this type of analysis. The National Institutes of Health (NIH) Toolbox, part of the NIH Neuroscience Blueprint Initiative, is a brief comprehensive battery of assessment tools being developed to measure cognitive, motor, sensory, and emotional function over the full range of normal function.[430] It is an example of a standardized assessment tool that has the potential to improve uniformity of assessment and make synthesis of results from multiple studies more meaningful.

Using a more standard battery of measures, it may be possible to better identify individual measures or domains of cognition that predict progression to clinically significant cognitive impairment (e.g., MCI or AD). Performance on these measures could be used to identify individuals at greater risk of decline in the near term.

More work is needed to better characterize and validate the various subtypes of CIND and MCI to be able to identify specific cognitive measures or domains of cognition that predict progression to AD. These findings could be used to enrich intervention samples with individuals at highest risk of progressing to dementia.

Finally, more research is needed to determine size of effect necessary to be of clinical significance, and this information should be used when interpreting results. In addition, measurement of meaningful change needs to include assessment of practice effects.

Identifying Differential Effects of Risk Factors in Subgroups and Interactions

Issues. Due to lack of data, we were not able to address whether there were important subgroup differences or interactions in the association between factors and cognitive outcomes. Even when studies reported that an interaction effect was not statistically significant, often the relevant information to determine if the study had statistical power to detect an interaction effect was not provided. Important subgroups where differential risk and differential effect of interventions are sometimes observed include sex, ethnic groups, and specific genes.

Addressing the gap. Observational studies should be powered to look at the differences between subgroups and interaction effects. Interactions may be present for specific individual characteristics or between exposure factors. The effects of exposures and interventions may depend on individual characteristics, so assessing the sample as a whole may hide effects. The use of a standard assessment battery (as suggested above) would allow for combining studies so that no single study would need to be sufficiently powered to examine differences among multiple subgroups.

Publication Bias

Issues. Most large epidemiological studies of aging ask questions about many of the same exposures. Depression and diabetes are examples of conditions that are not only routinely inquired about, but also show the most consistent association with AD and cognitive decline. In contrast, it is as striking that many of the large cohort studies have not published reports on the topic of the association between depression or diabetes and AD. It is possible that these other studies have investigated these exposures in their data and that the lack of publication on the finding means that they did not find a significant association. This suggests the potential for important publication bias.

Addressing the gap. One idea for addressing this gap would be to establish a registry of cohort studies that includes planned analyses. Although establishing a registry of cohort studies would be more challenging than creating the registries of clinical trials, it would allow the planned versus published results to be tracked to get a sense of publication bias. This would require the cooperation of journal editors and funding agencies to provide incentives to researchers to submit their data to the registry. In addition, statistical techniques for identifying publication bias in observational studies need to be developed and validated.

Determining the Cost and Benefit of Intervention

Issues. There is a lack of information on the overall effectiveness and the cost-effectiveness of the interventions. To date, the few RCTs conducted on the factors of interest here have not shown a positive effect of the intervention. However, once evidence is available to indicate

efficacy of an intervention, further research will need to be done to determine the effectiveness of the intervention from multiple perspectives.

Addressing the gap. Demonstrating an association between an intervention and a cognitive outcome in an RCT provides an indication of efficacy, but that is just the first step in evaluating the benefit of an intervention. From that point, the effectiveness of the intervention on many levels will need to be determined. Typically, effectiveness research has focused on the outcomes of cognitive decline and decline in performance of daily activities by the patient, but research in the area of pharmacoeconomics has shown that other outcomes should also be assessed when estimating the cost-benefit values of AD interventions.[431] These additional outcomes include not only others related to the patient, such as the presence and severity of neuropsychiatric and other behavioral symptoms, but may also include factors related to caregiver burden. These factors include the extent of care needed, whether providing care has required the caregiver to leave the workforce, and the impact on physical and mental health of providing care.

Some of the interventions suggested by this review (e.g lipid lowering agents) have been shown to have net benefit for other outcomes (e.g., cardiovascular). Evidence for a positive effect on cognition would simply be one more reason to use the intervention. But the additional benefit on cognition would also alter the cost-effectiveness ratio. In these situations, it will also be important to assess whether the threshold for effectiveness is the same for both outcomes (i.e., the cognitive outcome and the other outcome). It is possible that there may be a threshold effect or curvilinear effect for the intervention (e.g., glucose control for DM), and that these may differ for the two outcomes, which would influence recommendations for intervention intensity.

Chapter 4. Discussion

Alzheimer's disease (AD) is unique in that it may be the only late-life disease that has a long "silent" prodromal phase, no validated biological test for diagnosis, and imprecise measures of correlation between progression of phenotype and progression of pathology. Diagnosis during life is based on the clinical phenotype of symptom progression, which is heterogeneous between individuals. Part of the variation in clinical presentation may be due to the presence of other types of neuropathological changes in the brain in addition to those typically considered to be AD-related. These characteristics make it difficult not only to accurately diagnose AD but also to identify risk or protective factors for the disease; they also make it challenging to implement interventions efficiently and economically. The impact of these challenges is made clear by the fact that few of the putative risk or protective factors covered in this review had sufficient evidence from which to draw firm conclusions about their effect on AD and cognitive decline. But these findings need to be interpreted in the context of the effect size of a treatment or intervention that would make a noticeable difference in the disease burden. Using analytical models, it has been shown that relatively small delays in the onset of AD or the progression of the disease would have a large effect on the prevalence of the disease. A 1-year delay in both onset of AD and progression of AD would decrease the number of prevalent AD cases in 2050 by 9.19 million. This reduction in the number of AD cases is almost entirely due to fewer individuals with late-stage dementia, the point in the disease course when many individuals with AD are institutionalized and when the most care is needed.[432]

Many of the exposures reviewed in this report likely do not work in isolation in their effect on risk of AD or cognitive decline. Instead, they work in combination with other factors. Thus, the ideal interventions should be multi-dimensional, combining interventions for multiple risk factors and controlling for many other factors. But as noted when discussing the Key Question 6 in Chapter 3, above, few of the exposures reviewed here are appropriate for randomized controlled trials (RCTs). Among those that are not appropriate for intervention trials are exposures that one would want to avoid due to their negative impact on outcomes other than cognition. For example, smoking, diabetes, hypertension, and few years of education are all factors that have deleterious effects on health and lifestyle. Although healthcare interventions may be appropriate for some other potential influential factors (e.g., omega-3 fatty acids, statins, cognitive engagement), many of the other factors may be most appropriately addressed through public policy interventions (e.g., education, designing communities to facilitate physical activity) and public health interventions (educational campaigns on diet). Public education campaigns to change behavior to incorporate or exclude these factors would have relatively less risk (cost) to individuals.

One of the key limiting factors in synthesizing the current literature is the lack of standardization of exposure and outcome measures. Because outcome measures for cognitive decline were not standardized across studies, we limited the use of studies with continuous outcome measures when the conclusions from these studies were consistent with those from studies with categorical outcome measures. This meant that some studies reporting continuous measures were not reported in detail in this report, and the results of these studies were not synthesized quantitatively, but we do not think that this changed the conclusions for any exposure factor. In the future, more standardization at various steps of the research process is needed before all available data can be synthesized. We also acknowledge that standardization

can have its weaknesses and can limit innovations that may advance science. The key is to strike a balance between enough uniformity to maximize the use of study results and methods that are novel enough to advance the field to the next level.

Issues related to age are central to the interpretation of all of these results. The incidence of AD increases markedly with age, doubling in rate approximately every 5 years. Due to this, the age distribution of a study sample influences the expected number of AD cases; that is, the older the sample, the greater number of cases of AD expected. For this reason, the age distribution also influences the statistical power present to detect an association between an exposure and AD. Complicating this issue further, the neuropathological evidence available suggests that both typical AD pathology and microvascular changes in the brain become more frequent with age, so the older the sample, the more likely it is that mixed pathologies are present and contribute to the cognitive profile. However, the phenotype of the mixed pathology is often difficult to distinguish from that of AD pathology alone, meaning that the clinical AD group may become more heterogeneous with advancing age. The increasing incidence of AD with age also can affect the interpretation of studies of cognitive decline. The older the sample, the more likely it is that cognitive decline represents prodromal AD, and thus any association with a risk exposure may reflect an association with AD, not just cognitive decline.

Age may also be a central issue in regard to the timing of the exposure. There may be a window of time during which exposures influence risk of AD. For example, obesity in mid-life may be associated with increased risk of AD, while obesity in late life may be associated with reduced risk of disease. The latter finding may be explained by the weight loss often associated with the disease itself. But the point is clear that different exposures may have effects at different times along the life course or the natural history of AD. Ideally the exposure should be measured in different age groups within the same study to control for inter-study variability in measurement, but this may not be realistic given the long period of followup necessary when studying exposures in mid-life. Interventions may also have different effects at different points throughout life or the AD process. Although one might assume that interventions or lifestyle modification should be undertaken as early as possible, there may be other windows during which a given intervention may exert its effect. Careful consideration of the complex relation of exposure, age, and disease will likely be key to understanding the factors that alter risk of AD and cognitive decline.

The present review has some limitations. By excluding small to moderate observational studies and small RCTs, we may have missed some important evidence, particularly for factors with scant data. To evaluate the potential impact of excluding small studies, we coded detailed reasons for exclusion in a subset of citations. Of 549 citations, only three observational studies and two randomized controlled trials were excluded solely for small sample size. Applying these rates to the 6713 citations identified overall from electronic searching, we may have excluded as many as 48 articles for small sample size that otherwise would have met our eligibility criteria. However, small RCTs and systematic reviews based on small RCTs are more prone to bias, including publication bias and failure of randomization. Small observational studies have limited power. For factors where we have large studies already, it is very unlikely that the addition of small studies would change the estimate of effect or conclusions.

The exclusion of RCTs lasting less than 1 year may have missed some studies showing promising short-term results. These would not have been adequate to conclude that the intervention was useful for preventing cognitive decline or AD, but may have provided the impetus to conduct longer trials.

The extant research for a specific factor generally did not include more than a couple of studies using the same cognitive measure for a continuous outcome. Given the variability in outcome measures and the limited resources and time to complete the present project, it was not possible to perform quantitative meta-analyses on studies with continuous outcomes. We acknowledge, however, that quantitative estimates of effect may have been easier to interpret than qualitative syntheses.

The focus of this review was on the association between specific conditions (e.g., diabetes mellitus) and AD or cognitive decline. We did not evaluate the association between AD or cognitive decline and the treatments or interventions for the conditions. These exposures are of potential interest, but were not specified by the planning committee.

We note that this is a difficult literature to search for several reasons, including the wide range of factors assessed, the lack of well-validated search strategies for relevant observational studies, variability in categorizing studies by standard search terms, and variability in the terms used to categorize cognitive decline. For all these reasons, it is possible that relevant studies were overlooked.

Epidemiological studies of complex diseases using observational data often simultaneously evaluate the association between a range of exposures and the outcome of interest, in this case, AD or cognitive decline. These studies do not typically design their analyses specific to one or two factors of interest. We were not able to assess systematically how this approach may influence the association between the factor of interest and the outcome, but we note the issue as one to be considered when interpreting the results.

In summary, previous work on the search for clues to factors that alter the risk of AD and cognitive decline has provided a number of potential leads. These leads now need to be pursued with potentially novel approaches and increasingly rigorous scientific methods to be able to identify a real signal among the numerous factors throughout the life course that may contribute to the complex late-life disorders considered in this report.

Chapter 5. Conclusions

Among the many factors examined in this review, only some are amenable to being evaluated in randomized controlled trials (RCTs), and only a subset of these have actually been studied in high-quality RCTs as potential interventions for preventing or delaying the onset of Alzheimer's disease (AD) and cognitive decline. Effects of interventions in important subgroups, such as minority populations, were evaluated infrequently. A few of the factors considered in this report have shown potential promise in observational studies for both AD and cognitive decline, and in RCTs for at least one of the outcomes of interest. Moreover, several of the factors reviewed have demonstrated benefits beyond the potential of preserved cognition; that is, they promote overall health. Thus, there may be other reasons to recommend an intervention (e.g., increased physical activity) while further research is completed on its role in cognition.

The most general conclusions of this evidence report are summarized in Tables 74 and 75. These conclusions are based on a systematic review of the evidence for each factor, and on judgments about the quality of that evidence made using principles developed by the GRADE working group (www.gradeworkinggroup.org). For each factor examined, we considered the entire body of evidence and summarized the quality of that evidence as low, moderate, or high. The GRADE approach assigns an initial rating of "low" quality to observational studies and "high" quality to RCTs. These initial ratings may be modified by considerations relating to: detailed study design, consistency, strength of association, dose-response effect, directness, precision, and consideration of all plausible residual confounders that could reduce a demonstrated effect. Note that even within a given rating level, the quality of evidence may vary substantially; for example, there is considerable variability within the "low" quality level.

Tables 74 and 75 list, for AD and cognitive decline, respectively, the potential risk factors and interventions considered in this report, the associations observed between them and the outcome of interest (if any), and the quality of evidence supporting those associations. The tables also list factors for which the evidence was insufficient to establish whether or not an association exists. It is noteworthy that this last category includes many of the risk factors examined in this report.

In addition to sparse evidence, the extant research literature has other important limitations. Needed advances in study design and reporting include validated measures of exposure, pre-specified exposure categorizations, longer term trials, reporting of power calculations, and an agreed-upon battery of cognitive measures. Improving research design and reporting in these and other ways could improve confidence in observed associations and targeting of potential interventions. Conducting trials initially in those at high risk (e.g., those with mild cognitive impairment) would be an efficient approach. Well-designed, long-term cohort studies with robust measures of exposure and cognitive outcomes are needed to address the factors for which there is a strong biological mechanism or preliminary clinical evidence to suggest an important association.

Table 74. Summary of findings on potential risk factors and interventions for AD

Direction of association	Factors	Level of evidence‡
Increased risk	• APOE e4 genotype • Conjugated equine estrogen with methyl progesterone*	Moderate
	• Some non-steroidal anti-inflammatory drugs* • Depressive disorder • Diabetes mellitus • Hyperlipidemia in mid-life • Traumatic brain injury in males • Pesticide exposure • Never married, less social support • Current tobacco use	Low
Decreased risk	• Mediterranean diet • Folic acid • HMG-CoA reductase inhibitors (statins) • Higher levels of education • Light to moderate alcohol intake • Cognitively engaging activities • Physical activity, particularly high levels	Low
No association	• Ginkgo biloba*	High
	• Vitamin E* • Cholinesterase inhibitors*	Moderate
	• Anti-hypertensive medication* • Conjugated equine estrogen • Omega-3 fatty acids* • Vitamins B12, C, beta-carotene • Homocysteine • Hypertension • Obesity • Metabolic syndrome • Early childhood factors • Occupational level • Lead	Low
Inadequate evidence to assess association	• Saturated fat intake • Fruit and vegetable intake • Trace metals • High caloric intake • Memantine • Sleep apnea • Anxiety disorders • Resiliency • Non-cognitive, non-physical leisure activities • Agent Orange, Gulf War Syndrome • Solvents, aluminum • Genetic factors other than APOE	(Not applicable)

* Data from observational studies and RCTs.
Abbreviations: APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; RCTs = randomized controlled trials
‡GRADE criteria (see text)

Table 75. Summary of findings on potential risk factors and interventions for cognitive decline

Direction of association	Factors	Level of evidence‡
Increased risk	• APOE e4 genotype • Low plasma selenium • Depressive disorder • Diabetes mellitus • Metabolic syndrome • Current tobacco use	Low
Decreased risk	• Cognitive training*	High
	• Vegetable intake • Mediterranean diet • Omega-3 fatty acids* • Physical activity* • Non-cognitive, non-physical leisure activities	Low
No association	• Vitamin C, Vitamin E, beta-carotene supplements* • Conjugated equine estrogen* • HMG-CoA reductase inhibitors (statins)*	High
	• Aspirin* • Dehydroepiandosterone* • Cholinesterase inhibitors* • Multivitamin supplement* • Vitamins B6, B12 and folic acid supplements*	Moderate
	• Alcohol intake • Non-steroidal anti-inflammatory drugs*† • Anti-hypertensive medication* • Homocysteine • Hyperlipidemia • Anxiety disorders • Hypertension • Obesity • Early childhood factors • Higher levels of education • Social network, social supports	Low
Inadequate evidence to assess association	• Trace metals • Fat intake • High caloric intake • Gingko biloba* • Memantine • Sleep apnea • Resiliency • Occupational level • Traumatic brain injury • Toxic environmental exposures • Agent Orange, Gulf War Syndrome • Genetic factors other than APOE	(Not applicable)

*Data from observational studies and RCTs.
† Not associated with decreased risk but may be associated with increased risk.
Abbreviations: APOE = apolipoprotein E gene; APOE e4 = epsilon 4 allele of the apolipoprotein E gene; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; RCTs = randomized controlled trials
‡GRADE criteria (see text)

References

1. Alzheimer's Association. 2009 Alzheimer's disease facts and figures. Alzheimer's & Dementia 2009;5(3):234-70.
2. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health 1998;88(9):1337-42.
3. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 2007;29(1-2):125-32.
4. Hebert LE, Scherr PA, Bienias JL, et al. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003;60(8):1119-22.
5. Alzheimer's Disease International. World Alzheimer Report 2009. Available at :http://www.alz.co.uk/research/files/World%20Alzheimer%20Report.pdf. Accessed on September 30, 2009. 2009.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised. Washington, DC: American Psychiatric Association; 1987.
7. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34(7):939-44.
8. World Health Organization. International statistical classification of diseases and related health problems, Tenth Edition. Geneva: World Health Organization; 1992. Chapter V, categories F00-F99, Mental behavioural and developmental disorders, clinical description and diagnostic guidelines.
9. American Psychiatric Association. Dignostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
10. Duyckaerts C, Delatour B, Potier MC, et al. Classification and basic pathology of Alzheimer disease. Acta Neuropathol (Berl) 2009;118(1):5-36.
11. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of cognitive impairment without dementia in the United States.[summary for patients in Ann Intern Med. 2008 Mar 18;148(6):I-53; PMID: 18347348]. Ann Intern Med 2008;148(6):427-34.
12. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome.[erratum appears in Arch Neurol 1999 Jun;56(6):760]. Arch Neurol 1999;56(3):303-8.
13. Bynum JP, Rabins PV, Weller W, et al. The relationship between a dementia diagnosis, chronic illness, medicare expenditures, and hospital use. J Am Geriatr Soc 2004;52(2):187-94.
14. Eaker ED, Vierkant RA, Mickel SF, et al. Predictors of nursing home admission and/or death in incident Alzheimer's disease and other dementia cases compared to controls: a population-based study. J Clin Epidemiol 2002;55(5):462-8.
15. Evans DA, Smith LA, Scherr PA, et al. Risk of death from Alzheimer's disease in a community population of older persons. Am J Epidemiol 1991;134(4):403-12.
16. Helmer C, Joly P, Letenneur L, et al. Mortality with dementia: results from a French prospective community-based cohort. Am J Epidemiol 2001;154(7):642-8.
17. Schulz R, O'Brien AT, Bookwala J, et al. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. Gerontologist 1995;35(6):771-91.
18. Moore MJ, Zhu CW, Clipp EC. Informal costs of dementia care: estimates from the National Longitudinal Caregiver Study. Journals of Gerontology Series B-Psychological Sciences & Social Sciences 2001;56(4):S219-28.
19. Heron M, Hoyert D, Xu J, et al. Deaths: Preliminary data for 2006. National vital statistics reports; vol 56 no 16. Hyattsville, MD: National Center for Health Statistics; 2008.
20. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18(4):351-7.
21. Launer LJ, Brock DB. Population-based studies of AD: message and methods: an epidemiologic view. Stat Med 2004;23(2):191-7.
22. Irie F, Masaki KH, Petrovitch H, et al. Apolipoprotein E epsilon4 allele genotype and the effect of depressive symptoms on the risk of dementia in men: the Honolulu-Asia Aging Study. Arch Gen Psychiatry 2008;65(8):906-12.
23. Wilson RS, Barnes LL, Bennett DA, et al. Proneness to psychological distress and risk of Alzheimer disease in a biracial community. Neurology 2005;64(2):380-2.
24. Agency for Healthcare Research and Quality. Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 [Draft posted Oct. 2007]. Rockville, MD:Agency for Healthcare Research and Quality. Available at: http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf. Accessed September 3, 2009.
25. Wang C, Chung M, Balk E, et al. Effects of Omega-3 Fatty Acids on Cardiovascular Disease. Evidence Report/Technology Assessment No. 94 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center, under Contract No. 290-02-0022). AHRQ Publication No. 04-E009-2. Rockville, MD: Agency for Healthcare Research and Quality. March 2004. Available at: http://www.ahrq.gov/downloads/pub/evidence/pdf/o3cardio/o3cardio.pdf. Accessed May 8, 2009.

26. Myers E, McCrory D, Mills A, et al. Effectiveness of Assisted Reproductive Technology. Evidence Report/Technology Assessment No. 167 (Prepared by the Duke University Evidence-based Practice Center under Contract No. 290-02-0025.) AHRQ Publication No. 08-E012. Rockville, MD:Agency for Healthcare Research and Quality. May 2008. Available at: http://www.ahrq.gov/downloads/pub/evidence/pdf/infertility/infertility.pdf. Accessed May 8, 2009.
27. Juni P, Witschi A, Bloch R, et al. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999;282(11):1054-60.
28. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. BMJ 1998;316(7125):140-4.
29. Fotuhi M, Mohassel P, Yaffe K, et al. Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association. Nature Clinical Practice Neurology 2009;5(3):140-52.
30. Issa AM, Mojica WA, Morton SC, et al. The efficacy of omega-3 fatty acids on cognitive function in aging and dementia: a systematic review. Dement Geriatr Cogn Disord 2006;21(2):88-96.
31. Lim WS, Gammack JK, Van Niekerk J, et al. Omega 3 fatty acid for the prevention of dementia. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD005379. DOI: 10.1002/14651858.CD005379.pub2.
32. Balk E, Chung M, Raman G, et al. B Vitamins and Berries and Age-Related Neurodegenerative Disorders. Evidence Report/Technology Assessment No. 134. (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 06-E008. Rockville, MD: Agency for Healthcare Research and Quality. April 2006. Available at: http://www.ahrq.gov/downloads/pub/evidence/pdf/berry/berry.pdf. Accessed September 18, 2009. 2006.
33. McGuinness B, Craig D, Bullock R, et al. Statins for the prevention of dementia. Cochrane Database of Systematic Reviews 2009, Issue 2. Art, No.: CD003160. DOI: 10.1002/14651858.CD003160.pub2.
34. McGuinness B, Todd S, Passmore P, et al. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia (Review). Cochrane Database of Systematic Reviews 2006(2):CD004034.
35. Szekely CA, Thorne JE, Zandi PP, et al. Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. Neuroepidemiology 2004;23(4):159-69.
36. Grimley Evans J, Malouf R, Huppert F, et al. Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. Cochrane Database of Systematic Reviews 2006(4):CD006221.
37. Lethaby A, Hogervorst E, Richards M, et al. Hormone replacement therapy for cognitive function in postmenopausal women.[update of Cochrane Database Syst Rev. 2002;(3):CD003122; PMID: 12137675]. Cochrane Database of Systematic Reviews 2008(1):CD003122.
38. LeBlanc ES, Janowsky J, Chan BK, et al. Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 2001;285(11):1489-99.
39. Nickelsen T, Lufkin EG, Riggs BL, et al. Raloxifene hydrochloride, a selective estrogen receptor modulator: safety assessment of effects on cognitive function and mood in postmenopausal women. Psychoneuroendocrinology 1999;24(1):115-28.
40. Anstey KJ, Lipnicki DM, Low L-F. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. Am J Geriatr Psychiatry 2008;16(5):343-54.
41. Biessels GJ, Staekenborg S, Brunner E, et al. Risk of dementia in diabetes mellitus: a systematic review.[erratum appears in Lancet Neurol. 2006 Feb;5(2):113]. Lancet Neurology 2006;5(1):64-74.
42. Lu FP, Lin KP, Kuo HK, et al. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. PLoS ONE [Electronic Resource] 2009;4(1):e4144.
43. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. Diabetologia 2005;48(12):2460-9.
44. Raschetti R, Albanese E, Vanacore N, et al. Cholinesterase inhibitors in mild cognitive impairment: a systematic review of randomised trials. PLoS Medicine / Public Library of Science 2007;4(11):e338.
45. Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 2006;63(5):530-8.
46. Fleminger S, Oliver DL, Lovestone S, et al. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry 2003;74(7):857-62.
47. Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obes Rev 2008;9(3):204-18.
48. Angevaren M, Aufdemkampe G, Verhaar HJJ, et al. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment.[update of Cochrane Database Syst Rev. 2008;(2):CD005381; PMID: 18425918]. Cochrane Database of Systematic Reviews 2008(3):CD005381.
49. Caamano-Isorna F, Corral M, Montes-Martinez A, et al. Education and dementia: a meta-analytic study. Neuroepidemiology 2006;26(4):226-32.
50. Anstey KJ, von Sanden C, Salim A, et al. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol 2007;166(4):367-78.
51. Anstey KJPD, Mack HAPD, Cherbuin NPD. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. Am J Geriatr Psychiatry 2009;17(7):542-555.

52. Santibanez M, Bolumar F, Garcia AM, et al. Occupational risk factors in Alzheimer's disease: a review assessing the quality of published epidemiological studies. Occup Environ Med 2007;64(11):723-32.
53. Bertram L, McQueen MB, Mullin K, et al. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. Nat Genet 2007;39(1):17-23.
54. Luchsinger JA, Tang MX, Miller J, et al. Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. Arch Neurol 2007;64(1):86-92.
55. Morris MC, Evans DA, Schneider JA, et al. Dietary folate and vitamins B-12 and B-6 not associated with incident Alzheimer's disease. J Alzheimers Dis 2006;9(4):435-43.
56. Morris MC, Evans DA, Bienias JL, et al. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. J Neurol Neurosurg Psychiatry 2004;75(8):1093-9.
57. Ravaglia G, Forti P, Maioli F, et al. Homocysteine and folate as risk factors for dementia and Alzheimer disease. Am J Clin Nutr 2005;82(3):636-43.
58. Wang HX, Wahlin A, Basun H, et al. Vitamin B(12) and folate in relation to the development of Alzheimer's disease. Neurology 2001;56(9):1188-94.
59. Morris MC, Tangney CC, Bienias JL, et al. Validity and reproducibility of a food frequency questionnaire by cognition in an older biracial sample. Am J Epidemiol 2003;158(12):1213-7.
60. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 2002;287(24):3223-9.
61. Commenges D, Scotet V, Renaud S, et al. Intake of flavonoids and risk of dementia. Eur J Epidemiol 2000;16(4):357-63.
62. Fillenbaum GG, Kuchibhatla MN, Hanlon JT, et al. Dementia and Alzheimer's disease in community-dwelling elders taking vitamin C and/or vitamin E. Ann Pharmacother 2005;39(12):2009-14.
63. Gray SL, Anderson ML, Crane PK, et al. Antioxidant vitamin supplement use and risk of dementia or Alzheimer's disease in older adults. J Am Geriatr Soc 2008;56(2):291-5.
64. Laurin D, Masaki KH, Foley DJ, et al. Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol 2004;159(10):959-67.
65. Luchsinger JA, Tang MX, Shea S, et al. Antioxidant vitamin intake and risk of Alzheimer disease. Arch Neurol 2003;60(2):203-8.
66. Masaki KH, Losonczy KG, Izmirlian G, et al. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. Neurology 2000;54(6):1265-72.
67. Maxwell CJ, Hicks MS, Hogan DB, et al. Supplemental use of antioxidant vitamins and subsequent risk of cognitive decline and dementia. Dement Geriatr Cogn Disord 2005;20(1):45-51.
68. Morris MC, Beckett LA, Scherr PA, et al. Vitamin E and vitamin C supplement use and risk of incident Alzheimer disease. Alzheimer Dis Assoc Disord 1998;12(3):121-6.
69. Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. JAMA 2002;287(24):3230-7.
70. Morris MC, Evans DA, Tangney CC, et al. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. Am J Clin Nutr 2005;81(2):508-14.
71. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 2004;61(1):82-8.
72. Kalmijn S, Launer LJ, Ott A, et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 1997;42(5):776-82.
73. Barberger-Gateau P, Letenneur L, Deschamps V, et al. Fish, meat, and risk of dementia: cohort study. BMJ 2002;325(7370):932-3.
74. Laurin D, Verreault R, Lindsay J, et al. Omega-3 fatty acids and risk of cognitive impairment and dementia. J Alzheimers Dis 2003;5(4):315-22.
75. Morris MC, Evans DA, Bienias JL, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003;60(7):940-6.
76. Huang TL, Zandi PP, Tucker KL, et al. Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4. Neurology 2005;65(9):1409-14.
77. Schaefer EJ, Bongard V, Beiser AS, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol 2006;63(11):1545-50.
78. Barberger-Gateau P, Raffaitin C, Letenneur L, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology 2007;69(20):1921-30.
79. Samieri C, Feart C, Letenneur L, et al. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk. Am J Clin Nutr 2008;88(3):714-21.
80. Devore EE, Grodstein F, van Rooij FJ, et al. Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. Am J Clin Nutr 2009;90(1):170-6.
81. Kroger E, Verreault R, Carmichael PH, et al. Omega-3 fatty acids and risk of dementia: the Canadian Study of Health and Aging. Am J Clin Nutr 2009;90(1):184-92.
82. Morris MC, Evans DA, Bienias JL, et al. Dietary fats and the risk of incident Alzheimer disease. Arch Neurol 2003;60(2):194-200.
83. Laitinen MH, Ngandu T, Rovio S, et al. Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study. Dement Geriatr Cogn Disord 2006;22(1):99-107.
84. Scarmeas N, Stern Y, Tang MX, et al. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 2006;59(6):912-21.

85. Scarmeas N, Luchsinger JA, Schupf N, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA 2009;302(6):627-37.
86. Scarmeas N, Stern Y, Mayeux R, et al. Mediterranean diet and mild cognitive impairment. Arch Neurol 2009;66(2):216-25.
87. Feart C, Samieri C, Rondeau V, et al. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA 2009;302(6):638-48.
88. Hughes TF, Andel R, Small BJ, et al. Midlife fruit and vegetable consumption and risk of dementia in later life in Swedish twins. Am J Geriatr Psychiatry 2009;epub date 2009/11/17. DOI: 10.1097/JGP.0b013e3181c65250.
89. Dai Q, Borenstein AR, Wu Y, et al. Fruit and vegetable juices and Alzheimer's disease: the Kame Project. Am J Med 2006;119(9):751-9.
90. Luchsinger JA, Tang MX, Shea S, et al. Caloric intake and the risk of Alzheimer disease. Arch Neurol 2002;59(8):1258-63.
91. Yamada M, Kasagi F, Sasaki H, et al. Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. J Am Geriatr Soc 2003;51(3):410-4.
92. Curb JD, Rodriguez BL, Abbott RD, et al. Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. Neurology 1999;52(5):971-5.
93. Akomolafe A, Beiser A, Meigs JB, et al. Diabetes mellitus and risk of developing Alzheimer disease: results from the Framingham Study. Arch Neurol 2006;63(11):1551-5.
94. Hayden KM, Zandi PP, Lyketsos CG, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. Alzheimer Dis Assoc Disord 2006;20(2):93-100.
95. Irie F, Fitzpatrick AL, Lopez OL, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the Cardiovascular Health Study Cognition Study. Arch Neurol 2008;65(1):89-93.
96. Xu WL, von Strauss E, Qiu CX, et al. Uncontrolled diabetes increases the risk of Alzheimer's disease: a population-based cohort study. Diabetologia 2009;52(6):1031-9.
97. Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. Arterioscler Thromb Vasc Biol 2000;20(10):2255-60.
98. Muller M, Tang MX, Schupf N, et al. Metabolic syndrome and dementia risk in a multiethnic elderly cohort. Dement Geriatr Cogn Disord 2007;24(3):185-92.
99. Borenstein AR, Wu Y, Mortimer JA, et al. Developmental and vascular risk factors for Alzheimer's disease. Neurobiol Aging 2005;26(3):325-34.
100. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 2001;322(7300):1447-51.
101. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005;62(10):1556-60.
102. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging 2000;21(1):49-55.
103. Li G, Rhew IC, Shofer JB, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. J Am Geriatr Soc 2007;55(8):1161-7.
104. Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 2002;156(5):445-53.
105. Luchsinger JA, Reitz C, Honig LS, et al. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology 2005;65(4):545-51.
106. Posner HB, Tang MX, Luchsinger J, et al. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology 2002;58(8):1175-81.
107. Qiu C, Winblad B, Fastbom J, et al. Combined effects of APOE genotype, blood pressure, and antihypertensive drug use on incident AD. Neurology 2003;61(5):655-60.
108. Shah RC, Wilson RS, Bienias JL, et al. Relation of blood pressure to risk of incident Alzheimer's disease and change in global cognitive function in older persons. Neuroepidemiology 2006;26(1):30-6.
109. Morris MC, Scherr PA, Hebert LE, et al. Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. Arch Neurol 2001;58(10):1640-6.
110. Freitag MH, Peila R, Masaki K, et al. Midlife pulse pressure and incidence of dementia: the Honolulu-Asia Aging Study. Stroke 2006;37(1):33-7.
111. Tan ZS, Seshadri S, Beiser A, et al. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. Arch Intern Med 2003;163(9):1053-7.
112. Stewart R, White LR, Xue QL, et al. Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol 2007;64(1):103-7.
113. Kivipelto M, Helkala EL, Laakso MP, et al. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease.[summary for patients in Ann Intern Med. 2002 Aug 6;137(3):I-18; PMID: 12160384]. Ann Intern Med 2002;137(3):149-55.
114. Notkola IL, Sulkava R, Pekkanen J, et al. Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. Neuroepidemiology 1998;17(1):14-20.
115. Li G, Shofer JB, Kukull WA, et al. Serum cholesterol and risk of Alzheimer disease: a community-based cohort study. Neurology 2005;65(7):1045-50.

116. Reitz C, Tang M-X, Luchsinger J, et al. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol 2004;61(5):705-14.
117. Slooter AJ, Cruts M, Ott A, et al. The effect of APOE on dementia is not through atherosclerosis: the Rotterdam Study. Neurology 1999;53(7):1593-5.
118. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. Neurology 1995;45(6):1161-8.
119. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346(7):476-83.
120. Luchsinger JA, Tang MX, Shea S, et al. Plasma homocysteine levels and risk of Alzheimer disease. Neurology 2004;62(11):1972-6.
121. Blasko I, Jellinger K, Kemmler G, et al. Conversion from cognitive health to mild cognitive impairment and Alzheimer's disease: prediction by plasma amyloid beta 42, medial temporal lobe atrophy and homocysteine. Neurobiol Aging 2008;29(1):1-11.
122. Luchsinger JA, Patel B, Tang M-X, et al. Measures of adiposity and dementia risk in elderly persons. Arch Neurol 2007;64(3):392-8.
123. Whitmer RA, Gunderson EP, Quesenberry CP, Jr., et al. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr Alzheimer Res 2007;4(2):103-9.
124. Atti AR, Palmer K, Volpato S, et al. Late-life body mass index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. J Am Geriatr Soc 2008;56(1):111-6.
125. Hughes TF, Borenstein AR, Schofield E, et al. Association between late-life body mass index and dementia: The Kame Project. Neurology 2009;72(20):1741-6.
126. Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol 2009;66(3):336-42.
127. Graves AB, White E, Koepsell TD, et al. The association between head trauma and Alzheimer's disease. Am J Epidemiol 1990;131(3):491-501.
128. Rasmusson DX, Brandt J, Martin DB, et al. Head injury as a risk factor in Alzheimer's disease. Brain Inj 1995;9(3):213-9.
129. Broe GA, Henderson AS, Creasey H, et al. A case-control study of Alzheimer's disease in Australia. Neurology 1990;40(11):1698-707.
130. Amaducci LA, Fratiglioni L, Rocca WA, et al. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. Neurology 1986;36(7):922-31.
131. Chandra V, Kokmen E, Schoenberg BS, et al. Head trauma with loss of consciousness as a risk factor for Alzheimer's disease. Neurology 1989;39(12):1576-8.
132. Chandra V, Philipose V, Bell PA, et al. Case-control study of late onset "probable Alzheimer's disease". Neurology 1987;37(8):1295-300.
133. Forster DP, Newens AJ, Kay DW, et al. Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: a case-control study in northern England. J Epidemiol Community Health 1995;49(3):253-8.
134. Ferini-Strambi L, Smirne S, Garancini P, et al. Clinical and epidemiological aspects of Alzheimer's disease with presenile onset: a case control study. Neuroepidemiology 1990;9(1):39-49.
135. Fratiglioni L, Ahlbom A, Viitanen M, et al. Risk factors for late-onset Alzheimer's disease: a population-based, case-control study. Ann Neurol 1993;33(3):258-66.
136. Li G, Shen YC, Li YT, et al. A case-control study of Alzheimer's disease in China. Neurology 1992;42(8):1481-8.
137. Anonymous. The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. Neurology 1994;44(11):2073-80.
138. Mortimer JA, French LR, Hutton JT, et al. Head injury as a risk factor for Alzheimer's disease. Neurology 1985;35(2):264-7.
139. O'Meara ES, Kukull WA, Sheppard L, et al. Head injury and risk of Alzheimer's disease by apolipoprotein E genotype. Am J Epidemiol 1997;146(5):373-84.
140. Tsolaki M, Fountoulakis K, Chantzi E, et al. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of a Greek population. Int Psychogeriatr 1997;9(3):327-41.
141. van Duijn CM, Tanja TA, Haaxma R, et al. Head trauma and the risk of Alzheimer's disease. Am J Epidemiol 1992;135(7):775-82.
142. Mehta KM, Ott A, Kalmijn S, et al. Head trauma and risk of dementia and Alzheimer's disease: The Rotterdam Study. Neurology 1999;53(9):1959-62.
143. Plassman BL, Havlik RJ, Steffens DC, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 2000;55(8):1158-66.
144. Andersen K, Lolk A, Kragh-Sorensen P, et al. Depression and the risk of Alzheimer disease. Epidemiology 2005;16(2):233-8.
145. Dal Forno G, Palermo MT, Donohue JE, et al. Depressive symptoms, sex, and risk for Alzheimer's disease. Ann Neurol 2005;57(3):381-7.
146. Li YS, Meyer JS, Thornby J. Longitudinal follow-up of depressive symptoms among normal versus cognitively impaired elderly. Int J Geriatr Psychiatry 2001;16(7):718-27.
147. Palsson S, Aevarsson O, Skoog I. Depression, cerebral atrophy, cognitive performance and incidence of dementia. Population study of 85-year-olds. Br J Psychiatry 1999;174:249-53.
148. Steffens DC, Welsh-Bohmer KA, Burke JR, et al. Methodology and preliminary results from the neurocognitive outcomes of depression in the elderly study. J Geriatr Psychiatry Neurol 2004;17(4):202-11.
149. Lu PH, Edland SD, Teng E, et al. Donepezil delays progression to AD in MCI subjects with depressive symptoms. Neurology 2009;72(24):2115-21.

150. Gatz JL, Tyas SL, St John P, et al. Do depressive symptoms predict Alzheimer's disease and dementia? J Gerontol A Biol Sci Med Sci 2005;60(6):744-7.
151. Geerlings MI, den Heijer T, Koudstaal PJ, et al. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. Neurology 2008;70(15):1258-64.
152. Luchsinger JA, Honig LS, Tang MX, et al. Depressive symptoms, vascular risk factors, and Alzheimer's disease. Int J Geriatr Psychiatry 2008;23(9):922-8.
153. Arvanitakis Z, Schneider J, Wilson R, et al. Statins, incident Alzheimer disease, change in cognitive function, and neuropathology. Neurology 2008;70(19 Pt 2):1795-802.
154. Haag M, Hofman A, Koudstaal P, et al. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. J Neurol Neurosurg Psychiatry 2009;80(1):13-7.
155. Li G, Higdon R, Kukull WA, et al. Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. Neurology 2004;63(9):1624-8.
156. Li G, Larson E, Sonnen J, et al. Statin therapy is associated with reduced neuropathologic changes of Alzheimer disease. Neurology 2007;69(9):878-85.
157. Rea T, Breitner J, Psaty B, et al. Statin use and the risk of incident dementia: the Cardiovascular Health Study. Arch Neurol 2005;62(7):1047-51.
158. Zandi P, Sparks D, Khachaturian A, et al. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. Arch Gen Psychiatry 2005;62(2):217-24.
159. Sparks D, Kryscio R, Sabbagh M, et al. Reduced risk of incident AD with elective statin use in a clinical trial cohort. Curr Alzheimer Res 2008;5(4):416-21.
160. Guo Z, Fratiglioni L, Viitanen M, et al. Apolipoprotein E genotypes and the incidence of Alzheimer's disease among persons aged 75 years and older: variation by use of antihypertensive medication? Am J Epidemiol 2001;153(3):225-31.
161. in't Veld BA, Ruitenberg A, Hofman A, et al. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiol Aging 2001;22(3):407-12.
162. Khachaturian AS, Zandi PP, Lyketsos CG, et al. Antihypertensive medication use and incident Alzheimer disease: the Cache County Study. Arch Neurol 2006;63(5):686-92.
163. Peila R, White LR, Masaki K, et al. Reducing the risk of dementia: efficacy of long-term treatment of hypertension. Stroke 2006;37(5):1165-70.
164. Yasar S, Corrada M, Brookmeyer R, et al. Calcium channel blockers and risk of AD: the Baltimore Longitudinal Study of Aging. Neurobiol Aging 2005;26(2):157-63.
165. Haag MD, Hofman A, Koudstaal PJ, et al. Duration of antihypertensive drug use and risk of dementia: A prospective cohort study. Neurology 2009;72(20):1727-34.
166. Zandi PP, Anthony JC, Hayden KM, et al. Reduced incidence of AD with NSAID but not H2 receptor antagonists: the Cache County Study. Neurology 2002;59(6):880-6.
167. in't Veld BA, Ruitenberg A, Hofman A, et al. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. N Engl J Med 2001;345(21):1515-21.
168. Stewart WF, Kawas C, Corrada M, et al. Risk of Alzheimer's disease and duration of NSAID use. Neurology 1997;48(3):626-32.
169. Arvanitakis Z, Grodstein F, Bienias JL, et al. Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology. Neurology 2008;70(23):2219-25.
170. Cornelius C, Fastbom J, Winblad B, et al. Aspirin, NSAIDs, risk of dementia, and influence of the apolipoprotein E epsilon 4 allele in an elderly population. Neuroepidemiology 2004;23(3):135-43.
171. Szekely CA, Breitner JC, Fitzpatrick AL, et al. NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type. Neurology 2008;70(1):17-24.
172. Breitner JC, Haneuse SJ, Walker R, et al. Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. Neurology 2009;72(22):1899-905.
173. Wilson RS, Scherr PA, Hoganson G, et al. Early life socioeconomic status and late life risk of Alzheimer's disease. Neuroepidemiology 2005;25(1):8-14.
174. Karp A, Kareholt I, Qiu C, et al. Relation of education and occupation-based socioeconomic status to incident Alzheimer's disease. Am J Epidemiol 2004;159(2):175-83.
175. Letenneur L, Gilleron V, Commenges D, et al. Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. J Neurol Neurosurg Psychiatry 1999;66(2):177-83.
176. Stern Y, Gurland B, Tatemichi TK, et al. Influence of education and occupation on the incidence of Alzheimer's disease. JAMA 1994;271(13):1004-10.
177. Cobb JL, Wolf PA, Au R, et al. The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham Study. Neurology 1995;45(9):1707-12.
178. Ott A, van Rossum CT, van Harskamp F, et al. Education and the incidence of dementia in a large population-based study: the Rotterdam Study. Neurology 1999;52(3):663-6.
179. Scarmeas N, Levy G, Tang MX, et al. Influence of leisure activity on the incidence of Alzheimer's disease. Neurology 2001;57(12):2236-42.
180. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. Arch Neurol 2002;59(11):1737-46.
181. Di Carlo A, Baldereschi M, Amaducci L, et al. Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy. The ILSA Study. J Am Geriatr Soc 2002;50(1):41-8.

182. Ngandu T, von Strauss E, Helkala EL, et al. Education and dementia: what lies behind the association? Neurology 2007;69(14):1442-50.
183. Tyas SL, Salazar JC, Snowdon DA, et al. Transitions to mild cognitive impairments, dementia, and death: findings from the Nun Study. Am J Epidemiol 2007;165(11):1231-8.
184. Evans DA, Hebert LE, Beckett LA, et al. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. Arch Neurol 1997;54(11):1399-405.
185. Helmer C, Letenneur L, Rouch I, et al. Occupation during life and risk of dementia in French elderly community residents. J Neurol Neurosurg Psychiatry 2001;71(3):303-9.
186. Qiu C, Karp A, von Strauss E, et al. Lifetime principal occupation and risk of Alzheimer's disease in the Kungsholmen project. Am J Ind Med 2003;43(2):204-11.
187. Helmer C, Damon D, Letenneur L, et al. Marital status and risk of Alzheimer's disease: a French population-based cohort study. Neurology 1999;53(9):1953-8.
188. Wilson RS, Krueger KR, Arnold SE, et al. Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry 2007;64(2):234-40.
189. Fratiglioni L, Wang HX, Ericsson K, et al. Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000;355(9212):1315-9.
190. Hakansson K, Rovio S, Helkala EL, et al. Association between mid-life marital status and cognitive function in later life: population based cohort study. BMJ 2009;339:b2462.
191. Saczynski JS, Pfeifer LA, Masaki K, et al. The effect of social engagement on incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol 2006;163(5):433-40.
192. Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 2002;287(6):742-8.
193. Wilson RS, Scherr PA, Schneider JA, et al. Relation of cognitive activity to risk of developing Alzheimer disease. Neurology 2007;69(20):1911-20.
194. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. N Engl J Med 2003;348(25):2508-16.
195. Akbaraly TN, Portet F, Fustinoni S, et al. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology 2009;73(11):854-61.
196. Andel R, Crowe M, Pedersen NL, et al. Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins. J Gerontol A Biol Sci Med Sci 2008;63(1):62-6.
197. Abbott RD, White LR, Ross GW, et al. Walking and dementia in physically capable elderly men. JAMA 2004;292(12):1447-53.
198. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006;144(2):73-81.
199. Laurin D, Verreault R, Lindsay J, et al. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 2001;58(3):498-504.
200. Rovio S, Kareholt I, Helkala EL, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol 2005;4(11):705-11.
201. Rovio S, Kareholt I, Viitanen M, et al. Work-related physical activity and the risk of dementia and Alzheimer's disease. Int J Geriatr Psychiatry 2007;22(9):874-82.
202. Podewils LJ, Guallar E, Kuller LH, et al. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. Am J Epidemiol 2005;161(7):639-51.
203. Ravaglia G, Forti P, Lucicesare A, et al. Physical activity and dementia risk in the elderly: findings from a prospective Italian study. Neurology 2008;70(19 Pt 2):1786-94.
204. Peters R, Poulter R, Warner J, et al. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatr 2008;8:36.
205. Broe GA, Creasey H, Jorm AF, et al. Health habits and risk of cognitive impairment and dementia in old age: a prospective study on the effects of exercise, smoking and alcohol consumption. Aust N Z J Public Health 1998;22(5):621-3.
206. Juan D, Zhou DHD, Li J, et al. A 2-year follow-up study of cigarette smoking and risk of dementia. Eur J Neurol 2004;11(4):277-82.
207. Launer LJ, Andersen K, Dewey ME, et al. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology 1999;52(1):78-84.
208. Merchant C, Tang MX, Albert S, et al. The influence of smoking on the risk of Alzheimer's disease. Neurology 1999;52(7):1408-12.
209. Moffat SD, Zonderman AB, Metter EJ, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology 2004;62(2):188-93.
210. Wang HX, Fratiglioni L, Frisoni GB, et al. Smoking and the occurrence of Alzheimer's disease: cross-sectional and longitudinal data in a population-based study. Am J Epidemiol 1999;149(7):640-4.
211. Aggarwal NT, Bienias JL, Bennett DA, et al. The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. Neuroepidemiology 2006;26(3):140-6.
212. Reitz C, den Heijer T, van Duijn C, et al. Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. Neurology 2007;69(10):998-1005.
213. Deng J, Zhou DH, Li J, et al. A 2-year follow-up study of alcohol consumption and risk of dementia. Clin Neurol Neurosurg 2006;108(4):378-83.
214. Huang W, Qiu C, Winblad B, et al. Alcohol consumption and incidence of dementia in a community sample aged 75 years and older. J Clin Epidemiol 2002;55(10):959-64.

215. Larrieu S, Letenneur L, Helmer C, et al. Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort. Journal of Nutrition, Health & Aging 2004;8(3):150-4.
216. Luchsinger JA, Tang MX, Siddiqui M, et al. Alcohol intake and risk of dementia. J Am Geriatr Soc 2004;52(4):540-6.
217. Mukamal KJ, Kuller LH, Fitzpatrick AL, et al. Prospective study of alcohol consumption and risk of dementia in older adults. JAMA 2003;289(11):1405-13.
218. Ruitenberg A, van Swieten JC, Witteman JC, et al. Alcohol consumption and risk of dementia: the Rotterdam Study. Lancet 2002;359(9303):281-6.
219. Shin IS, Stewart R, Kim JM, et al. Mitochondrial aldehyde dehydrogenase polymorphism is not associated with incidence of Alzheimer's disease. Int J Geriatr Psychiatry 2005;20(11):1075-80.
220. Ganguli M, Vander Bilt J, Saxton JA, et al. Alcohol consumption and cognitive function in late life: a longitudinal community study. Neurology 2005;65(8):1210-7.
221. Espeland MA, Gu L, Masaki KH, et al. Association between reported alcohol intake and cognition: results from the Women's Health Initiative Memory Study. Am J Epidemiol 2005;161(3):228-38.
222. Tyas SL, Manfreda J, Strain LA, et al. Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. Int J Epidemiol 2001;30(3):590-7.
223. Baldi I, Lebailly P, Mohammed-Brahim B, et al. Neurodegenerative diseases and exposure to pesticides in the elderly. Am J Epidemiol 2003;157(5):409-14.
224. Gauthier E, Fortier I, Courchesne F, et al. Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study. Environ Res 2001;86(1):37-45.
225. Salib E, Hillier V. A case-control study of Alzheimer's disease and aluminium occupation. Br J Psychiatry 1996;168(2):244-9.
226. Gun RT, Korten AE, Jorm AF, et al. Occupational risk factors for Alzheimer disease: a case-control study. Alzheimer Dis Assoc Disord 1997;11(1):21-7.
227. Graves AB, Rosner D, Echeverria D, et al. Occupational exposures to solvents and aluminium and estimated risk of Alzheimer's disease. Occup Environ Med 1998;55(9):627-33.
228. Rondeau V, Jacqmin-Gadda H, Commenges D, et al. Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol 2009;169(4):489-96.
229. Kennedy AM, Brown J, Rossor M. The genetics of Alzheimer's disease. Baillieres Clin Neurol 1994;3(2):217-40.
230. Breitner JC, Welsh KA, Gau BA, et al. Alzheimer's disease in the National Academy of Sciences-National Research Council Registry of Aging Twin Veterans. III. Detection of cases, longitudinal results, and observations on twin concordance. Arch Neurol 1995;52(8):763-71.
231. Pedersen NL, Gatz M, Berg S, et al. How heritable is Alzheimer's disease late in life? Findings from Swedish twins. Ann Neurol 2004;55(2):180-5.
232. Gatz M, Pedersen NL, Berg S, et al. Heritability for Alzheimer's disease: the study of dementia in Swedish twins. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 1997;52(2):M117-25.
233. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997;278(16):1349-56.
234. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease.[Erratum appears in Nat Genet. 2009 Oct;41(10):1156]. Nat Genet 2009;41(10):1088-93.
235. Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet 2009;41(10):1094-9.
236. Morris MC, Evans DA, Bienias JL, et al. Dietary folate and vitamin B12 intake and cognitive decline among community-dwelling older persons. Arch Neurol 2005;62(4):641-5.
237. Clarke R, Birks J, Nexo E, et al. Low vitamin B-12 status and risk of cognitive decline in older adults. Am J Clin Nutr 2007;86(5):1384-91.
238. Kado DM, Karlamangla AS, Huang MH, et al. Homocysteine versus the vitamins folate, B6, and B12 as predictors of cognitive function and decline in older high-functioning adults: MacArthur Studies of Successful Aging. Am J Med 2005;118(2):161-7.
239. de Lau LM, Smith AD, Refsum H, et al. Plasma vitamin B12 status and cerebral white-matter lesions. J Neurol Neurosurg Psychiatry 2009;80(2):149-57.
240. Fotuhi M, Zandi PP, Hayden KM, et al. Better cognitive performance in elderly taking antioxidant vitamins E and C supplements in combination with nonsteroidal anti-inflammatory drugs: the Cache County Study. Alzheimers Dement 2008;4(3):223-7.
241. Morris MC, Evans DA, Bienias JL, et al. Vitamin E and cognitive decline in older persons. Arch Neurol 2002;59(7):1125-32.
242. Wengreen HJ, Munger RG, Corcoran CD, et al. Antioxidant intake and cognitive function of elderly men and women: the Cache County Study. J Nutr Health Aging 2007;11(3):230-7.
243. Kang JH, Grodstein F. Plasma carotenoids and tocopherols and cognitive function: a prospective study. Neurobiol Aging 2008;29(9):1394-403.
244. Kalmijn S, Feskens EJ, Launer LJ, et al. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol 1997;145(1):33-41.
245. Berr C, Balansard B, Arnaud J, et al. Cognitive decline is associated with systemic oxidative stress: the EVA study. Etude du Vieillissement Arteriel. J Am Geriatr Soc 2000;48(10):1285-91.
246. Morris MC, Evans DA, Tangney CC, et al. Fish consumption and cognitive decline with age in a large community study. Arch Neurol 2005;62(12):1849-53.

247. van Gelder BM, Tijhuis M, Kalmijn S, et al. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. Am J Clin Nutr 2007;85(4):1142-7.
248. Heude B, Ducimetiere P, Berr C. Cognitive decline and fatty acid composition of erythrocyte membranes--The EVA Study. Am J Clin Nutr 2003;77(4):803-8.
249. Beydoun MA, Kaufman JS, Satia JA, et al. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr 2007;85(4):1103-11.
250. Beydoun MA, Kaufman JS, Sloane PD, et al. n-3 Fatty acids, hypertension and risk of cognitive decline among older adults in the Atherosclerosis Risk in Communities (ARIC) study. Public Health Nutr 2008;11(1):17-29.
251. Dullemeijer C, Durga J, Brouwer IA, et al. n 3 fatty acid proportions in plasma and cognitive performance in older adults. Am J Clin Nutr 2007;86(5):1479-85.
252. Morris MC, Evans DA, Bienias JL, et al. Dietary fat intake and 6-year cognitive change in an older biracial community population. Neurology 2004;62(9):1573-9.
253. Morris MC, Evans DA, Tangney CC, et al. Dietary copper and high saturated and trans fat intakes associated with cognitive decline. Arch Neurol 2006;63(8):1085-8.
254. Akbaraly TN, Hininger-Favier I, Carriere I, et al. Plasma selenium over time and cognitive decline in the elderly. Epidemiology 2007;18(1):52-8.
255. Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. Ann Neurol 2005;57(5):713-20.
256. Morris MC, Evans DA, Tangney CC, et al. Associations of vegetable and fruit consumption with age-related cognitive change. Neurology 2006;67(8):1370-6.
257. Cherbuin N, Reglade-Meslin C, Kumar R, et al. Risk factors of transition from normal cognition to mild cognitive disorder: the PATH through Life Study. Dement Geriatr Cogn Disord 2009;28(1):47-55.
258. Yaffe K, Fiocco AJ, Lindquist K, et al. Predictors of maintaining cognitive function in older adults: the Health ABC study. Neurology 2009;72(23):2029-35.
259. Comijs HC, Kriegsman DM, Dik MG, et al. Somatic chronic diseases and 6-year change in cognitive functioning among older persons. Arch Gerontol Geriatr 2009;48(2):191-6.
260. Knopman DS, Mosley TH, Catellier DJ, et al. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. Alzheimers Dement 2009;5(3):207-14.
261. Devore EE, Kang JH, Okereke O, et al. Physical activity levels and cognition in women with type 2 diabetes. Am J Epidemiol 2009;170(8):1040-7.
262. Carmelli D, Swan GE, Reed T, et al. Midlife cardiovascular risk factors, ApoE, and cognitive decline in elderly male twins. Neurology 1998;50(6):1580-5.
263. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 2004;292(18):2237-42.
264. van den Berg E, Biessels GJ, de Craen AJ, et al. The metabolic syndrome is associated with decelerated cognitive decline in the oldest old. Neurology 2007;69(10):979-85.
265. Ho RC, Niti M, Yap KB, et al. Metabolic syndrome and cognitive decline in chinese older adults: results from the singapore longitudinal ageing studies. Am J Geriatr Psychiatry 2008;16(6):519-22.
266. Solfrizzi V, Panza F, Colacicco AM, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology 2004;63(10):1882-91.
267. Tervo S, Kivipelto M, Hanninen T, et al. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dement Geriatr Cogn Disord 2004;17(3):196-203.
268. Reitz C, Tang MX, Manly J, et al. Hypertension and the risk of mild cognitive impairment. Arch Neurol 2007;64(12):1734-40.
269. Alves de Moraes S, Szklo M, Knopman D, et al. The relationship between temporal changes in blood pressure and changes in cognitive function: atherosclerosis risk in communities (ARIC) study. Prev Med 2002;35(3):258-63.
270. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56(1):42-8.
271. Barnes DE, Cauley JA, Lui LY, et al. Women who maintain optimal cognitive function into old age. J Am Geriatr Soc 2007;55(2):259-64.
272. Swan GE, DeCarli C, Miller BL, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. Neurology 1998;51(4):986-93.
273. Gurland BJ, Teresi J, Smith WM, et al. Effects of treatment for isolated systolic hypertension on cognitive status and depression in the elderly. J Am Geriatr Soc 1988;36(11):1015-22.
274. Haan MN, Shemanski L, Jagust WJ, et al. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA 1999;282(1):40-6.
275. Hebert LE, Scherr PA, Bennett DA, et al. Blood pressure and late-life cognitive function change: a biracial longitudinal population study. Neurology 2004;62(11):2021-4.
276. Insel KC, Palmer RF, Stroup-Benham CA, et al. Association between change in systolic blood pressure and cognitive decline among elderly Mexican Americans: data from the Hispanic established population for epidemiology study of the elderly. Exp Aging Res 2005;31(1):35-54.
277. Kuo HK, Jones RN, Milberg WP, et al. Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: a longitudinal analysis of the advanced cognitive training for independent and vital elderly cohort. J Am Geriatr Soc 2005;53(7):1154-61.

278. Tzourio C, Dufouil C, Ducimetiere P, et al. Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. Epidemiology of Vascular Aging. Neurology 1999;53(9):1948-52.
279. Waldstein SR, Giggey PP, Thayer JF, et al. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. Hypertension 2005;45(3):374-9.
280. Glynn RJ, Beckett LA, Hebert LE, et al. Current and remote blood pressure and cognitive decline. JAMA 1999;281(5):438-45.
281. Kivipelto M, Helkala EL, Hanninen T, et al. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology 2001;56(12):1683-9.
282. Kalmijn S, Feskens EJ, Launer LJ, et al. Cerebrovascular disease, the apolipoprotein e4 allele, and cognitive decline in a community-based study of elderly men. Stroke 1996;27(12):2230-5.
283. Reitz C, Luchsinger J, Tang MX, et al. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. Neurology 2005;64(8):1378-83.
284. Packard C, Westendorp R, Stott D, et al. Association between apolipoprotein E4 and cognitive decline in elderly adults. J Am Geriatr Soc 2007;55(11):1777-85.
285. Dufouil C, Alperovitch A, Ducros V, et al. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. Ann Neurol 2003;53(2):214-21.
286. Kalmijn S, Launer LJ, Lindemans J, et al. Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study. Am J Epidemiol 1999;150(3):283-9.
287. Sturman MT, de Leon CF, Bienias JL, et al. Body mass index and cognitive decline in a biracial community population. Neurology 2008;70(5):360-7.
288. Barnes DE, Alexopoulos GS, Lopez OL, et al. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. Arch Gen Psychiatry 2006;63(3):273-9.
289. Christensen H, Henderson AS, Korten AE, et al. ICD-10 mild cognitive disorder: its outcome three years later. Int J Geriatr Psychiatry 1997;12(5):581-6.
290. Dufouil C, Fuhrer R, Dartigues JF, et al. Longitudinal analysis of the association between depressive symptomatology and cognitive deterioration. Am J Epidemiol 1996;144(7):634-41.
291. Geda YE, Knopman DS, Mrazek DA, et al. Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: a prospective cohort study. Arch Neurol 2006;63(3):435-40.
292. Geerlings MI, Schoevers RA, Beekman AT, et al. Depression and risk of cognitive decline and Alzheimer's disease. Results of two prospective community-based studies in The Netherlands. Br J Psychiatry 2000;176:568-75.
293. Ng TP, Niti M, Zaw MH, et al. Depressive symptoms and incident cognitive impairment in cognitively well-functioning older men and women. J Am Geriatr Soc 2009;57(6):1058-63.
294. Panza F, D'Introno A, Colacicco AM, et al. Depressive symptoms, vascular risk factors and mild cognitive impairment. The Italian longitudinal study on aging. Dement Geriatr Cogn Disord 2008;25(4):336-46.
295. Paterniti S, Verdier-Taillefer MH, Dufouil C, et al. Depressive symptoms and cognitive decline in elderly people. Longitudinal study. Br J Psychiatry 2002;181:406-10.
296. Ravaglia G, Forti P, Lucicesare A, et al. Prevalent depressive symptoms as a risk factor for conversion to mild cognitive impairment in an elderly Italian cohort. Am J Geriatr Psychiatry 2008;16(10):834-43.
297. Wilson RS, Schneider JA, Boyle PA, et al. Chronic distress and incidence of mild cognitive impairment. Neurology 2007;68(24):2085-92.
298. Yaffe K, Blackwell T, Gore R, et al. Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. Arch Gen Psychiatry 1999;56(5):425-30.
299. Chodosh J, Kado DM, Seeman TE, et al. Depressive symptoms as a predictor of cognitive decline: MacArthur Studies of Successful Aging. Am J Geriatr Psychiatry 2007;15(5):406-15.
300. Comijs HC, Jonker C, Beekman AT, et al. The association between depressive symptoms and cognitive decline in community-dwelling elderly persons. Int J Geriatr Psychiatry 2001;16(4):361-7.
301. Dotson VM, Resnick SM, Zonderman AB. Differential association of concurrent, baseline, and average depressive symptoms with cognitive decline in older adults. Am J Geriatr Psychiatry 2008;16(4):318-30.
302. Ganguli M, Du Y, Dodge HH, et al. Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. Arch Gen Psychiatry 2006;63(2):153-60.
303. Gonzalez HM, Bowen ME, Fisher GG. Memory decline and depressive symptoms in a nationally representative sample of older adults: the Health and Retirement Study (1998-2004). Dement Geriatr Cogn Disord 2008;25(3):266-71.
304. Prince M, Lewis G, Bird A, et al. A longitudinal study of factors predicting change in cognitive test scores over time, in an older hypertensive population. Psychol Med 1996;26(3):555-68.
305. Rabbitt P, Lunn M, Ibrahim S, et al. Unhappiness, health and cognitive ability in old age. Psychol Med 2008;38(2):229-36.
306. Raji MA, Reyes-Ortiz CA, Kuo YF, et al. Depressive symptoms and cognitive change in older Mexican Americans. J Geriatr Psychiatry Neurol 2007;20(3):145-52.
307. Wilson RS, Mendes De Leon CF, Bennett DA, et al. Depressive symptoms and cognitive decline in a community population of older persons. J Neurol Neurosurg Psychiatry 2004;75(1):126-9.

308. Niti M, Yap KB, Kua EH, et al. APOE-epsilon4, depressive symptoms, and cognitive decline in Chinese older adults: Singapore Longitudinal Aging Studies. J Gerontol A Biol Sci Med Sci 2009;64(2):306-11.
309. Bierman EJ, Comijs HC, Rijmen F, et al. Anxiety symptoms and cognitive performance in later life: results from the longitudinal aging study Amsterdam. Aging Ment Health 2008;12(4):517-23.
310. Gallacher J, Bayer A, Fish M, et al. Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study. Psychosom Med 2009;71(6):659-66.
311. Wetherell JL, Reynolds CA, Gatz M, et al. Anxiety, cognitive performance, and cognitive decline in normal aging. J Gerontol B Psychol Sci Soc Sci 2002;57(3):P246-55.
312. Agostini JV, Tinetti ME, Han L, et al. Effects of statin use on muscle strength, cognition, and depressive symptoms in older adults. J Am Geriatr Soc 2007;55(3):420-5.
313. Bernick C, Katz R, Smith N, et al. Statins and cognitive function in the elderly: the Cardiovascular Health Study. Neurology 2005;65(9):1388-94.
314. Szwast SJ, Hendrie H, Lane K, et al. Association of statin use with cognitive decline in elderly African Americans. Neurology 2007;69(19):1873-80.
315. Hayden KM, Zandi PP, Khachaturian AS, et al. Does NSAID use modify cognitive trajectories in the elderly? The Cache County study. Neurology 2007;69(3):275-82.
316. Jonker C, Comijs HC, Smit JH. Does aspirin or other NSAIDs reduce the risk of cognitive decline in elderly persons? Results from a population-based study. Neurobiol Aging 2003;24(4):583-8.
317. Grodstein F, Skarupski KA, Bienias JL, et al. Anti-inflammatory agents and cognitive decline in a bi-racial population. Neuroepidemiology 2008;30(1):45-50.
318. Hee Kang J, Grodstein F. Regular use of nonsteroidal anti-inflammatory drugs and cognitive function in aging women. Neurology 2003;60(10):1591-7.
319. Ryan J, Carriere I, Scali J, et al. Life-time estrogen exposure and cognitive functioning in later life. Psychoneuroendocrinology 2009;34(2):287-98.
320. Everson-Rose SA, Mendes de Leon CF, Bienias JL, et al. Early life conditions and cognitive functioning in later life. Am J Epidemiol 2003;158(11):1083-9.
321. Graves AB, Rajaram L, Bowen JD, et al. Cognitive decline and Japanese culture in a cohort of older Japanese Americans in King County, WA: the Kame Project. J Gerontol B Psychol Sci Soc Sci 1999;54(3):S154-61.
322. Alvarado BE, Zunzunegui MV, Del Ser T, et al. Cognitive decline is related to education and occupation in a Spanish elderly cohort. Aging Clin Exp Res 2002;14(2):132-42.
323. Koster A, Penninx BW, Bosma H, et al. Socioeconomic differences in cognitive decline and the role of biomedical factors. Ann Epidemiol 2005;15(8):564-71.
324. Lee S, Buring JE, Cook NR, et al. The relation of education and income to cognitive function among professional women. Neuroepidemiology 2006;26(2):93-101.
325. Lee S, Kawachi I, Berkman LF, et al. Education, other socioeconomic indicators, and cognitive function. Am J Epidemiol 2003;157(8):712-20.
326. Kalmijn S, Feskens EJ, Launer LJ, et al. Longitudinal study of the effect of apolipoprotein e4 allele on the association between education and cognitive decline in elderly men. BMJ 1997;314(7073):34-5.
327. Manly JJ, Schupf N, Tang MX, et al. Cognitive decline and literacy among ethnically diverse elders. J Geriatr Psychiatry Neurol 2005;18(4):213-7.
328. Wilson RS, Hebert LE, Scherr PA, et al. Educational attainment and cognitive decline in old age. Neurology 2009;72(5):460-5.
329. Karlamangla AS, Miller-Martinez D, Aneshensel CS, et al. Trajectories of cognitive function in late life in the United States: demographic and socioeconomic predictors. Am J Epidemiol 2009;170(3):331-42.
330. Shadlen MF, Larson EB, Wang L, et al. Education modifies the effect of apolipoprotein epsilon 4 on cognitive decline. Neurobiol Aging 2005;26(1):17-24.
331. Christensen H, Batterham PJ, Mackinnon AJ, et al. The association of APOE genotype and cognitive decline in interaction with risk factors in a 65-69 year old community sample. BMC Geriatr 2008;8:14.
332. Winnock M, Letenneur L, Jacqmin-Gadda H, et al. Longitudinal analysis of the effect of apolipoprotein E epsilon4 and education on cognitive performance in elderly subjects: the PAQUID study. J Neurol Neurosurg Psychiatry 2002;72(6):794-7.
333. Potter GG, Plassman BL, Helms MJ, et al. Occupational characteristics and cognitive performance among elderly male twins. Neurology 2006;67(8):1377-82.
334. Virtanen M, Singh-Manoux A, Ferrie JE, et al. Long working hours and cognitive function: the Whitehall II Study. Am J Epidemiol 2009;169(5):596-605.
335. Yu F, Ryan LH, Schaie KW, et al. Factors associated with cognition in adults: the Seattle Longitudinal Study. Res Nurs Health 2009;32(5):540-50.
336. Barnes LL, Mendes de Leon CF, Wilson RS, et al. Social resources and cognitive decline in a population of older African Americans and whites. Neurology 2004;63(12):2322-6.
337. Holtzman RE, Rebok GW, Saczynski JS, et al. Social network characteristics and cognition in middle-aged and older adults. J Gerontol B Psychol Sci Soc Sci 2004;59(6):P278-84.
338. Green AF, Rebok G, Lyketsos CG. Influence of social network characteristics on cognition and functional status with aging. Int J Geriatr Psychiatry 2008;23(9):972-8.
339. Seeman TE, Lusignolo TM, Albert M, et al. Social relationships, social support, and patterns of cognitive aging in healthy, high-functioning older adults: MacArthur studies of successful aging. Health Psychol 2001;20(4):243-55.

340. Aartsen MJ, Van Tilburg T, Smits CH, et al. Does widowhood affect memory performance of older persons? Psychol Med 2005;35(2):217-26.
341. van Gelder BM, Tijhuis M, Kalmijn S, et al. Marital status and living situation during a 5-year period are associated with a subsequent 10-year cognitive decline in older men: the FINE Study. J Gerontol B Psychol Sci Soc Sci 2006;61(4):P213-9.
342. Ho SC, Woo J, Sham A, et al. A 3-year follow-up study of social, lifestyle and health predictors of cognitive impairment in a Chinese older cohort. Int J Epidemiol 2001;30(6):1389-96.
343. Zunzunegui MV, Alvarado BE, Del Ser T, et al. Social networks, social integration, and social engagement determine cognitive decline in community-dwelling Spanish older adults. J Gerontol B Psychol Sci Soc Sci 2003;58(2):S93-S100.
344. Muniz-Terrera G, Matthews F, Dening T, et al. Education and trajectories of cognitive decline over 9 years in very old people: methods and risk analysis. Age Ageing 2009;38(3):277-82.
345. Verghese J, LeValley A, Derby C, et al. Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. Neurology 2006;66(6):821-7.
346. Wilson RS, Bennett DA, Bienias JL, et al. Cognitive activity and cognitive decline in a biracial community population. Neurology 2003;61(6):812-6.
347. Bosma H, van Boxtel MP, Ponds RW, et al. Engaged lifestyle and cognitive function in middle and old-aged, non-demented persons: a reciprocal association? Z Gerontol Geriatr 2002;35(6):575-81.
348. Lytle ME, Vander Bilt J, Pandav RS, et al. Exercise level and cognitive decline: the MoVIES project. Alzheimer Dis Assoc Disord 2004;18(2):57-64.
349. Schuit AJ, Feskens EJ, Launer LJ, et al. Physical activity and cognitive decline, the role of the apolipoprotein e4 allele. Med Sci Sports Exerc 2001;33(5):772-7.
350. Yaffe K, Barnes D, Nevitt M, et al. A prospective study of physical activity and cognitive decline in elderly women: women who walk. Arch Intern Med 2001;161(14):1703-8.
351. Weuve J, Kang JH, Manson JE, et al. Physical activity, including walking, and cognitive function in older women. JAMA 2004;292(12):1454-61.
352. Niti M, Yap KB, Kua EH, et al. Physical, social and productive leisure activities, cognitive decline and interaction with APOE-epsilon 4 genotype in Chinese older adults. Int Psychogeriatr 2008;20(2):237-51.
353. Weisskopf MG, Wright RO, Schwartz J, et al. Cumulative lead exposure and prospective change in cognition among elderly men: the VA Normative Aging Study. Am J Epidemiol 2004;160(12):1184-93.
354. Launer LJ, Feskens EJ, Kalmijn S, et al. Smoking, drinking, and thinking. The Zutphen Elderly Study. Am J Epidemiol 1996;143(3):219-27.
355. Ott A, Andersen K, Dewey ME, et al. Effect of smoking on global cognitive function in nondemented elderly. Neurology 2004;62(6):920-4.
356. Whittington J, FA H. Smoking and cognitive decline. Human Psychopharmacology 1997;12:467-80.
357. Graves AB, Bowen JD, Rajaram L, et al. Impaired olfaction as a marker for cognitive decline: interaction with apolipoprotein E epsilon4 status. Neurology 1999;53(7):1480-7.
358. Lui L-Y, Stone K, Cauley JA, et al. Bone loss predicts subsequent cognitive decline in older women: the study of osteoporotic fractures. J Am Geriatr Soc 2003;51(1):38-43.
359. Paleologos M, Cumming RG, Lazarus R. Cohort study of vitamin C intake and cognitive impairment. Am J Epidemiol 1998;148(1):45-50.
360. Ford AB, Mefrouche Z, Friedland RP, et al. Smoking and cognitive impairment: a population-based study. J Am Geriatr Soc 1996;44(8):905-9.
361. Reitz C, Luchsinger J, Tang MX, et al. Effect of smoking and time on cognitive function in the elderly without dementia. Neurology 2005;65(6):870-5.
362. Dufouil C, Tzourio C, Brayne C, et al. Influence of apolipoprotein E genotype on the risk of cognitive deterioration in moderate drinkers and smokers. Epidemiology 2000;11(3):280-4.
363. Wright CB, Elkind MS, Luo X, et al. Reported alcohol consumption and cognitive decline: The northern Manhattan study. Neuroepidemiology 2006;27(4):201-7.
364. Stott DJ, Falconer A, Kerr GD, et al. Does low to moderate alcohol intake protect against cognitive decline in older people? J Am Geriatr Soc 2008;56(12):2217-24.
365. Solfrizzi V, D'Introno A, Colacicco AM, et al. Alcohol consumption, mild cognitive impairment, and progression to dementia. Neurology 2007;68(21):1790-9.
366. Wilson RS, Bienias JL, Berry-Kravis E, et al. The apolipoprotein E epsilon 2 allele and decline in episodic memory. J Neurol Neurosurg Psychiatry 2002;73(6):672-7.
367. Bretsky P, Guralnik JM, Launer L, et al. The role of APOE-epsilon4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. Neurology 2003;60(7):1077-81.
368. Blair CK, Folsom AR, Knopman DS, et al. APOE genotype and cognitive decline in a middle-aged cohort. Neurology 2005;64(2):268-76.
369. Staehelin HB, Perrig-Chiello P, Mitrache C, et al. Apolipoprotein E genotypes and cognitive functions in healthy elderly persons. Acta Neurol Scand 1999;100(1):53-60.
370. Yaffe K, Cauley J, Sands L, et al. Apolipoprotein E phenotype and cognitive decline in a prospective study of elderly community women. Arch Neurol 1997;54(9):1110-4.
371. Dik MG, Jonker C, Bouter LM, et al. APOE-epsilon4 is associated with memory decline in cognitively impaired elderly. Neurology 2000;54(7):1492-7.
372. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352(23):2379-88.

373. DeKosky ST, Williamson JD, Fitzpatrick AL, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA 2008;300(19):2253-62.
374. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 2003;21(5):875-86.
375. Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch Intern Med 1994;154(19):2154-60.
376. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998;352(9137):1347-51.
377. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med 2002;162(18):2046-52.
378. Thal LJ, Ferris SH, Kirby L, et al. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology 2005;30(6):1204-15.
379. Adapt Research Group, Lyketsos CG, Breitner JC, et al. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. Neurology 2007;68(21):1800-8.
380. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289(20):2651-62.
381. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004;291(24):2947-58.
382. Murthy A. A One-Year Multi-center, Randomized, Double-blind, Placebo-controlled Evaluation of the Efficacy and Safety of Donepezil Hydrochloride in Subjects with Mild Cognitive Impairment (MCI). Available at: http://www.clinicaltrials.gov/ct2/show/NCT00293176. Accessed on: September 24, 2009.
383. National Institute of Mental Health; University of Iowa. Cognitive Enhancers Explored with PET Imaging. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2009 Jul 09]. Available from: http://clinicaltrials.gov/ct/show/nct00042172. 2002.
384. Novartis. Efficacy and safety of Rivastigmine in patients with mild cognitive impairment. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2009 Jul 09]. Available from: http://clinicaltrials.gov/ct/show/nct00134953. 2005.
385. Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. Lancet Neurol 2007;6(6):501-12.
386. Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 2008;70(22):2024-35.
387. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352(23):2379-88.
388. Diniz BS, Pinto JA, Jr., Gonzaga ML, et al. To treat or not to treat? A meta-analysis of the use of cholinesterase inhibitors in mild cognitive impairment for delaying progression to Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci 2009;259(4):248-56.
389. Kang JH, Cook N, Manson J, et al. A trial of B vitamins and cognitive function among women at high risk of cardiovascular disease. Am J Clin Nutr 2008;88(6):1602-10.
390. McMahon JA, Green TJ, Skeaff CM, et al. A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med 2006;354(26):2764-72.
391. McNeill G, Avenell A, Campbell MK, et al. Effect of multivitamin and multimineral supplementation on cognitive function in men and women aged 65 years and over: a randomised controlled trial. Nutr J 2007;6:10.
392. Kang JH, Cook N, Manson J, et al. A randomized trial of vitamin E supplementation and cognitive function in women. Arch Intern Med 2006;166(22):2462-8.
393. Smith A, Clark R, Nutt D, et al. Anti-Oxidant Vitamins and Mental Performance of the Elderly. Human Psychopharmacology Clinical and Experimental 1999;14:459-471.
394. Kang JH, Cook NR, Manson JE, et al. Vitamin E, vitamin C, beta carotene, and cognitive function among women with or at risk of cardiovascular disease: The Women's Antioxidant and Cardiovascular Study. Circulation 2009;119(21):2772-80.
395. Dodge HH, Zitzelberger T, Oken BS, et al. A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. Neurology 2008;70(19 Pt 2):1809-17.
396. van de Rest O, Geleijnse JM, Kok FJ, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. Neurology 2008;71(6):430-8.
397. Dangour AD, Clemens F, Elbourne D, et al. A randomised controlled trial investigating the effect of n-3 long-chain polyunsaturated fatty acid supplementation on cognitive and retinal function in cognitively healthy older people: the Older People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study protocol [ISRCTN72331636]. Nutrition Journal 2006;5:20.

398. Quinn J. A randomized double-blind placebo-controlled trial of the effects of docosahexaenoic acid (DHA) in slowing the progression of Alzheimer's disease. Available at: http://clinicaltrials.gov/ct2/show/NCT00440050. Accessed September 9, 2009.
399. Yurko-Mauro K. A randomized double-blind placebo-controlled study to evaluate the effects of DHA on cognitive function in the elderly. Available at: http://clinicaltrials.gov/ct2/show/NCT00278135. Accessed September 9, 2009.
400. Vakhapova V. A single-center, open-label study to assess the efficacy of SharpPS(TM)-Gold in elderly subjects with memory impairment. Available at: http://clincaltrials.gov/ct2/show/NCT00736034. Accessed September 9, 2009.
401. Anonymous. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial.[summary for patients in Curr Cardiol Rep. 2002 Nov;4(6):486-7; PMID: 12379169]. Lancet 2002;360(9326):7-22.
402. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360(9346):1623-30.
403. Saxby BK, Harrington F, Wesnes KA, et al. Candesartan and cognitive decline in older patients with hypertension: a substudy of the SCOPE trial. Neurology 2008;70(19 Pt 2):1858-66.
404. Skoog I, Lithell H, Hansson L, et al. Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE). Am J Hypertens 2005;18(8):1052-9.
405. Prince MJ, Bird AS, Blizard RA, et al. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. BMJ 1996;312(7034):801-5.
406. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003;163(9):1069-75.
407. Lithell H, Hansson L, Skoog I, et al. The Study on COgnition and Prognosis in the Elderly (SCOPE); outcomes in patients not receiving add-on therapy after randomization. J Hypertens 2004;22(8):1605-12.
408. Di Bari M, Pahor M, Franse LV, et al. Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. Am J Epidemiol 2001;153(1):72-8.
409. Price JF, Stewart MC, Deary IJ, et al. Low dose aspirin and cognitive function in middle aged to elderly adults: randomised controlled trial. BMJ 2008;337:a1198.
410. Hee Kang J, Cook N, Manson J, et al. Low dose aspirin and cognitive function in the women's health study cognitive cohort. BMJ 2007;334(7601):987.
411. Martin BK, Szekely C, Brandt J, et al. Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. Arch Neurol 2008;65(7):896-905.
412. Tierney MC, Oh P, Moineddin R, et al. A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. Psychoneuroendocrinology 2009;34(7):1065-74.
413. Kritz-Silverstein D, von Muhlen D, Laughlin GA, et al. Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. J Am Geriatr Soc 2008;56(7):1292-8.
414. Koontz J, Baskys A. Effects of galantamine on working memory and global functioning in patients with mild cognitive impairment: a double-blind placebo-controlled study. Am J Alzheimers Dis Other Demen 2005;20(5):295-302.
415. Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. Neurology 2004;63(4):651-7.
416. Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurology 2009;72(18):1555-61.
417. Yesavage JA, Friedman L, Ashford JW, et al. Acetylcholinesterase inhibitor in combination with cognitive training in older adults. J Gerontol B Psychol Sci Soc Sci 2008;63(5):P288-94.
418. Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA 2006;296(23):2805-14.
419. Unverzagt FW, Kasten L, Johnson KE, et al. Effect of memory impairment on training outcomes in ACTIVE. J Int Neuropsychol Soc 2007;13(6):953-60.
420. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA 2002;288(18):2271-81.
421. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 2008;300(9):1027-37.
422. Caselli RJ, Dueck AC, Osborne D, et al. Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. N Engl J Med 2009;361(3):255-63.
423. Ambrosius W, Chew E. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. Available at: http://clinicaltrials.gov/ct2/show/NCT00542178. Accessed October 1, 2009.
424. Launer L. Action to Control Cardiovascular Risk in Diabetes -- Memory in Diabetes. Available at: http://clinicaltrials.gov/ct2/show/NCT00182910. Accessed October 1, 2009.

425. Ben-Shlomo Y, Kuh D, Ben-Shlomo Y, et al. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol 2002;31(2):285-93.
426. West SG, Duan N, Pequegnat W, et al. Alternatives to the randomized controlled trial. Am J Public Health 2008;98(8):1359-66.
427. Chatfield MD, Brayne CE, Matthews FE, et al. A systematic literature review of attrition between waves in longitudinal studies in the elderly shows a consistent pattern of dropout between differing studies. J Clin Epidemiol 2005;58(1):13-9.
428. Robinson KA, Dennison CR, Wayman DM, et al. Systematic review identifies number of strategies important for retaining study participants. J Clin Epidemiol 2007;60(8):757-65.
429. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Epidemiology 2007;18(6):800-4.
430. Gershon R. NIH Toolboox: Assessment of Neurological and Behavioral Function. Available at: http://www.nihtoolbox.org/default.aspx. Accessed October 1, 2009.
431. Wimo A, Winblad B, Stoffler A, et al. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. Pharmacoeconomics 2003;21(5):327-40.
432. Brookmeyer R, Johnson E, Ziegler-Graham K, et al. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 2007;3(3):186-91.

Acronyms and Abbreviations

3MS	Modified Mini-Mental State Examination
AA	Arachidonic acid
AACD	Aging-associated cognitive decline
AAMI	Age-associated memory impairment
ABI	Ankle-brachial index
ACE	Angiotensin 1 converting enzyme
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly trial
AD	Alzheimer's disease
ADAPT	Alzheimer's Disease Anti-inflammatory Prevention Trial
ADAS-Cog	Alzheimer Disease Assessment Scale-Cognitive subscale
ADEPT	Adult Development and Enrichment Project;
ADL(s)	Activities of daily living
AHRQ	Agency for Healthcare Research and Quality
aMCI	Amnestic mild cognitive impairment
ApoE	Apolipoprotein E protein
APOE	Apolipoprotein E gene
APOE e4	Epsilon 4 allele of the apolipoprotein E gene
APP	Amyloid precursor protein
ARIC	Atherosclerosis Risk in Communities study
ASA	Acetylsalicylate (aspirin)
AVLT	Auditory Verbal Learning Test
BDI	Beck Depression Inventory
BMI	Body mass index
BNT	Boston Naming Test
BP	Blood pressure
BSRT	Babcock Story Recall Test
BVRT	Benton Visual Retention Test
CAD	Coronary artery disease
CASI	Cognitive Abilities Screening Instrument
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-sum of boxes
CEE	Conjugated equine estrogen
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CES-D	Center for Epidemiologic Studies Depression scale
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CIND	Cognitive impairment not demented
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COWA	Controlled Oral Word Association test
CRP	C-reactive protein
CSI-D	Community Screening Interview for Dementia
CVA	Cerebrovascular accident

CVD	Cardiovascular disease
CVLT	California Verbal Learning Test
DBP	Diastolic blood pressure
DCT	Digit Cancellation Test
DHA	Docosahexaenoic acid
DHEA	Dehydroepiandosterone
DHP-CCB	Dihydropyridine-calcium channel blockers;
DM	Diabetes mellitus
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSST	Digit Symbol Substitution Test
DWR	Delayed word recall
EPA	Eicosapentaenoic acid
EPC	Evidence-based Practice Center
FTT	Finger Tapping Test
GDS	Geriatric Depression Scale
GEE	Generalized estimated equations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GWAS	Genome-wide association studies
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HDRS	Hamilton Depression Rating Scale
HDDS	Hasegawa Dementia Screening Scale
HFFQ	Harvard Food Frequency Questionnaire
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HMO	Health maintenance organization
HR	Hazard ratio
HRT	Hormone replacement therapy
HTN	Hypertension
IADL	Instrumental activities of daily living
IL-1B	Interleukin-1beta
IL-6	Interleukin-6
IQ	Intelligence quotient
JNC VII	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LDL	Low density lipoprotein
MAC	Memory assessment clinics
MCD	Mild cognitive disorder
MCI	Mild cognitive impairment
MDD	Major depressive disorder
MeSH	Medical Subject Heading
MI	Myocardial infarction
MMSE	Mini-Mental State Examination
MNC	Mild neurocognitive disorder
MPA	Medroxyprogesterone acetate
mTICS	modified Telephone interview for cognitive status
MUFA(s)	Monounsaturated fatty acid

NCEP-ATPIII	National Cholesterol Education Program 3rd Adult Treatment Panel Guideline
NIH	National Institutes of Health
NIMH	National Institutes of Mental Health
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association
NS	Not statistically significant
NSAID(s)	Non-steroidal anti-inflammatory drug(s)
NYU	New York University
OMAR	Office of Medical Applications of Research
OR	Odds ratio
PMA	Primary Mental Abilities
PUFA(s)	Polyunsaturated fatty acid(s)
PVD	Peripheral vascular disease
RCT	Randomized controlled trial
RERI	Relative excess risk from interaction
RR	Relative risk
RVLT	Rey Auditory Verbal Learning Test
SBP	Systolic blood pressure
SCOPE	Study on Cognition and Prognosis in the Elderly
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SE	Standard error
SERM	Selective estrogen receptor modulator
SES	Socioeconomic status
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SFA(s)	Saturated fatty acid(s)
SHEP	Systolic Hypertension in the Elderly Program
SNP	Single-nucleotide polymorphism
SPMSQ	Short Portable Mental Status Questionnaire
STAI	State Trait Anxiety Inventory
Syst-Eur	Systolic Hypertension in Europe trial
TBI	Traumatic brain injury
TEP	Technical expert panel
TFAM	Transcription factor A, mitochondrial
TIA	Transient ischemic attack
TICS	Telephone Interview for Cognitive Status
TICS-m	Telephone Interview for Cognitive Status (modified version)
TNK1	Tyrosine kinase, non-receptor 1
Trails A/B	Trail Making Test Part A/B
Trails B	Trail Making Test Part B
VA	United States Department of Veterans Affairs
VAD	Vascular Alzheimer's disease
VRT	Visual Reproduction Test (immediate and delayed recall) from the Wechsler Memory Scale
WAIS	Wechsler Adult Intelligence Scale

WAIS-R	Wechsler Adult Intelligence Scale-Revised
WF	Word Fluency Test
WMD	Weighted mean difference
WMS	Wechsler Memory Scale
WMS-R	Wechsler Memory Scale-Revised

Appendix A. Exact Search Strings

Our search strategy to identify systematic reviews combined terms specific to the risk factor or intervention, terms for Alzheimer's disease or cognitive impairment, and the PubMed filter for systematic reviews. We used a similar strategy in the Cochrane Database of Systematic Reviews.

1. (Terms for the exposures), AND
2. (Terms for the outcome of interest (AD or cognitive decline)), AND
3. Systematic[sb]

Our search strategy to identify original research combined terms specific to the risk factor or intervention, terms for Alzheimer's disease or cognitive impairment, and terms for the relevant study designs. We limited the search to studies in humans, age 45+, and published in English. We excluded studies conducted in special populations.

For KQ 1 and KQ2, we used the following general search strategy, utilizing the specific terms that follow:
1. (Terms for the exposures), AND
2. (Terms for the outcome of interest (AD or cognitive decline)), AND
3. (Terms for observational study designs)
4. NOT (*Terms for excluded non general population samples*)
5. NOT (Terms for excluded publication types)
6. Limits (Human, English, Age 45+)

For KQ 3 and KQ4, we used the following general search strategy, utilizing the specific terms that follow:
1. (Terms for the exposures), AND
2. (Terms for the outcome of interest (AD or cognitive decline)), AND
3. (Terms for randomized controlled trial study designs)
4. NOT (*Terms for excluded non general population samples*)
5. NOT (Terms for excluded publication types)
6. Limits (Human, English, Age 45+)

SPECIFIC SEARCH TERMS

KQ1 and KQ2: Terms for Exposures
Sleep apnea syndromes[Mesh] OR "sleep apnea"[tw] OR (obstructive[all fields] AND sleep[all fields] AND apnea[all fields])

Obesity[Mesh] OR overweight[mesh]

Diabetes mellitus[Mesh]

Intelligence tests[Mesh] or "IQ"[Title/abstract] OR "aptitude tests"[mesh]

Metabolic syndrome x[Mesh] OR insulin resistance[Mesh] OR Hyperinsulinism/*epidemiology/psychology

“TBI”[All fields] OR “traumatic brain injury”[All fields] OR (“traumatic” AND “brain” AND “injury”) OR craniocerebral trauma[mesh]

Hypertension[mesh]

Educational status[mesh]

Employment[mesh] OR "occupational status"[Title/abstract] OR retirement[mesh]

Literacy[tw] OR illiterate*[tw] OR illiteracy[tw] OR reading[mesh]

"Social Identification"[Mesh] OR "Social Isolation"[Mesh] OR "Social Desirability"[Mesh] OR "Social Adjustment"[Mesh] OR "Social Conformity"[Mesh] OR "Social Behavior"[Mesh:noexp] OR "Social Environment"[Mesh] OR “Interpersonal Relations"[Mesh:noexp] OR family conflict[mesh] OR (social AND (network* OR engage* OR participat*)) OR “marital status”[mesh]

(("Resilience, Psychological"[Mesh]) OR (resilienc*)) OR ((depressive disorder) OR (depression[MeSH])) OR (anxiety[MeSH] OR "anxiety disorders"[Mesh])

homocysteine[mesh] OR homocysteine[all fields] OR homocyst*[title/abstract]

smoking[MeSH] OR Nicotine[MeSH] OR (tobacco[All Fields] AND smoking[All Fields]) OR (Cigarette[All Fields] AND Smoking[All Fields])

Persian Gulf Syndrome[MeSH] OR (Gulf[All Fields] AND War[All Fields] AND Syndrome*[All Fields]) OR (Gulf[All Fields] AND War[All Fields] AND Illness*[All Fields])

Environmental Pollutants[MeSH] OR (Environmen*[All Fields] AND Pollut*[All Fields])

Agent Orange[substance name] OR Agent orange[all fields] OR tetrachlorodibenzodioxin[Mesh] OR tetrachlorodibenzodioxin[all fields] OR “2,4-Dichlorophenoxyacetic Acid”[mesh] OR “2.4,5-Trichlorophenoxyacetic Acid[all fields]

Pesticides[MeSH] OR Pesticides[All Fields]

((childhood[tw] OR child[tw] OR children[tw]) AND socioecono*[tw]) OR ((childhood[tw] OR child[tw] OR children[tw]) AND exposure*[tw]) OR ((childhood[tw] OR child[tw] OR children[tw]) AND “urban population”[Mesh]) OR ((childhood[tw] OR child[tw] OR children[tw]) AND “rural population”[Mesh])

KQ 1, KQ2, KQ3, KQ4: Terms for exposures and/or interventions

Dietary supplements[Mesh] OR “ginkgo biloba”[tw] OR “ginkgo biloba”[Mesh] OR pregnenolone[mesh] OR pregnenolone[tw] OR huperzine[tw]

Antioxidants[mesh] OR Antioxidants[pharmacological action] OR resveratrol[all fields] OR “ascorbic acid”[mesh] OR “vitamin e”[mesh] OR tocopherols[mesh]

Vitamins[Mesh] OR [pharmacological action] OR trace elements [pharmacological action]

Gonadal steroid hormones[mesh] OR Dehydroepiandrosterone[mesh] OR “DHEA”[title/abstract] OR leuprolide[mesh] OR leuprolide[tw] OR lupron[tw] OR “estrogens, conjugated (usp)"[MeSH Terms] OR premarin[tw] OR “conjugated estrogens”[all fields] OR gonadotropin*[tw] OR Phytoestrogens [Pharmacological Action]

“Nutritional status”[mesh] OR “nutrition assessment”[mesh] OR “diet therapy”[mesh] OR “diet, fat-restricted”[mesh] OR “diet, Mediterranean”[mesh] OR “Mediterranean diet”[all fields] OR “diet, vegetarian”[mesh] OR “diet, atherogenic”[mesh] OR “dietary fats”[mesh] OR fruit[mesh] OR vegetables[mesh] OR phytoestrogens[pharmacological action] OR “fatty acids, omega-3”[mesh] OR “fish oil”[tw]

Video games[mesh] OR puzzle*[tw] OR “memory training”[tw] OR “cognitive training”[tw] OR (“cognitive”[tw] AND “training”[tw])

(((((((("Diuretics"[Mesh] OR "Diuretics "[Pharmacological Action])) OR ("Calcium Channel Blockers"[Mesh] OR "Calcium Channel Blockers "[Pharmacological Action])) OR ("Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Angiotensin-Converting Enzyme Inhibitors "[Pharmacological Action])) OR ("Adrenergic alpha-Antagonists"[Mesh] OR "Adrenergic alpha-Antagonists "[Pharmacological Action])) OR ("Adrenergic beta-Antagonists"[Mesh] OR "Adrenergic beta-Antagonists "[Pharmacological Action])) OR ("Ganglionic Blockers"[Mesh] OR "Ganglionic Blockers "[Pharmacological Action])) OR ("Vasodilator Agents"[Mesh] OR "Vasodilator Agents "[Pharmacological Action]) AND ("Hypertension"[Mesh])) OR ("Antihypertensive Agents"[Mesh] OR "Antihypertensive Agents "[Pharmacological Action])

leisure activities[mesh] OR "leisure activity"[title/abstract] OR "leisure activities"[title/abstract] OR travel[mesh] OR travel[title/abstract]

exercise[mesh] OR "physical fitness"[mesh] OR running[mesh] OR swimming[mesh] OR walking[mesh]

(("Anti-Inflammatory Agents"[Mesh] OR "Anti-Inflammatory Agents "[Pharmacological Action])) OR ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Anti-Inflammatory Agents, Non-Steroidal "[Pharmacological Action])

(("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[MeSH Terms]) OR ("Hydroxymethylglutaryl-coa"[All fields] AND "reductase"[All fields] AND "inhibitors"[All fields]) OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[All fields] OR "statins"[All fields] OR "statin"[All fields] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Pharmacological Action] OR (rosuvastatin) OR (simvastatin) OR (pravastatin) OR (atorvastatin) OR (fluvastatin) OR (lovastatin) OR (cerivastatin) OR (compactin) OR (meglutol) OR ("red yeast rice" OR ("red" AND "yeast" AND "rice")))

(("Thiazolidinediones"[Mesh]) OR ("Metformin"[Mesh]) OR ("insulin-sensitivity"[All fields]) OR ("insulin-sensitizing"[All fields]) OR ("insulin"[All fields] AND ("sensitivity"[All fields] OR "sensitizing"[All fields]))) OR (metformin[all fields]) OR (Thiazolidinedione*[all fields])

"cholinergic antagonists"[MeSH Terms] OR "cholinergic antagonists"[Pharmacological Action]

((galantamine) OR (donepezil) OR (rivastigmine) OR (memantine))

KQ 1, KQ2, KQ3, KQ4: Terms for Observational study designs

((Epidemiologic Studies[Mesh:noexp] OR case-control studies[Mesh] OR cohort studies[Mesh] OR seroepidemiologic studies[Mesh]) OR cohort OR cohorts OR observ* OR case-control OR non-randomized OR nonrandomized OR unrandomized OR prospectiv* OR retrospectiv* OR follow* OR longitudinal OR (cases AND controls)) AND (odds ratio[Mesh] OR "odds ratio" OR "relative risk" OR risk OR risks OR associat* OR causality OR etiology OR epidemiology OR ethnology OR probability OR inciden*)

Because of the high degree of overlap between terms for emotional health factors cognitive decline, we limited the terms for observational study designs

((Epidemiologic Studies[Mesh:noexp] OR cohort studies[Mesh] OR follow* OR longitudinal) AND (odds ratio[Mesh] OR "odds ratio" OR "relative risk" OR risk OR risks OR inciden* OR etiology OR causality))

KQ 3, KQ4: Terms for RCTs (sensitive strategy)

((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

KQ 1, KQ 3: Terms for Alzheimers disease

Alzheimer* OR alzheimer disease[mesh]

KQ 2, KQ4: Terms for mild cognitive impairment or cognitive decline

(((cognitiv* OR cognition OR memory) AND (declin* OR impair* OR deteriora* OR change* OR deficit* OR complaint*)) OR "Cognition Disorders"[Mesh:noexp]) OR ("pre-clinical AD" OR "preclinical AD" OR "pre-clinical Alzheimer" OR "preclinical alzheimer")

KQ1, KQ2, KQ3, KQ4: Terms to exclude non general population or non-general medical samples

schizophrenia[mesh] OR schizophrenia[all fields] OR “down syndrome”[mesh] OR “down syndrome”[all fields] OR “psychotic disorders”[mesh] OR “psychosis”[all fields] OR "substance-related disorders"[MeSH Terms] OR “substance abuse”[all fields] OR epilepsy[mesh] OR epilepsy[all fields] OR “seizure disorder”[all fields] OR “Parkinson disease”[mesh] OR “Parkinson disease”[all fields]

***KQ1, KQ2, KQ3, KQ4: Terms to exclude selected* Publication types**

review, letter

***KQ1, KQ2, KQ3, KQ4:* Terms to Limit to the samples of interest**

human, English, age 45+

Appendix B. Evidence Tables

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Aartsen, Van Tilburg, Smits, et al., 2005 Longitudinal Aging Study of Amsterdam (LASA)	**Geographical location:** Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3105 participants enrolled for T1 of LASA. (Oversampled for men and older participants) 1144 participants enrolled for this analysis. **Duration of follow up:** 6 years. **Time from risk factor assessment to final cognitive assessment:** 6 years.	**Age:** Range: 60-85 **Sex:** [n (%)] Female: 474 (41.43) Male: 690 (58.57%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** All **Inclusion criteria:** Age >60 yrs Married at baseline **Exclusion criteria:** NR	**Risk factor/exposure 1:** Loss of spouse during the follow up period (1992-1998) **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Physical health at baseline Mental health at baseline. **Method(s) of assessing cognitive status:** Other – Recall of 15 words from the Auditory verbal learning test. **Informant interview?:** No	**1) Follow-up rate:** 3805 participants recruited in the first sample which was collected for a different study. Of this, 3107 participated in the T1 phase of the LASA study. Of the 698 who did not participate, 126 (18%) dies, 134 (19%) were too disabled to participate, 394 (56%) refused and 44 (6%) could not be contacted. 2545 (82%) participated in T2 and 2076 (67%) participated in T3. Of the participants in T1, 1144 met the inclusion criteria to be included in this analysis. **2) Important baseline differences:** Attrition of the sample was related to lower memory at baseline, being male, having chronic diseases or having lower functional ability. **3) Outcome of interest #1:** Memory decline was observed in 33% of the widowed men and 17% of the widowed women while one 17% of the non widowed men and 13% of non widowed women had memory decline. There was a statistically significant difference between widowed and non widowed men: χ^2= 6.6; p<0.05 but not for women χ^2= 2.3; p=0.13.	**Comments:** There were some baseline differences between the participants who were lost to follow up and those included in this analysis. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: No 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Can't Tell 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Abbott, White, Ross, et al., 2004 Honolulu Heart Program, Honolulu-Asia Aging Study (HAAS)	**Geographical location:** Honolulu, Hawaii **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** Initially 3734; Final sample of 2257. **Duration of follow up:** Mean "nearly" 7 years **Time from risk factor assessment to final cognitive assessment:** Mean "nearly" 7 years	**Age:** Mean (SD): Miles walked/day: <0.25: 77.4 (4.4) 0.25-1: 77.3 (4.2) <1-2: 76.6 (3.8) >2: 76.0 (3.6) **Sex:** Female: 0% Male: 100% **Race/ethnicity:** Japanese ancestry **Baseline cognitive status:** Non-demented **Inclusion criteria:** Survivors of the original Honolulu Heart Program cohort. Japanese ancestry. Men physically capable of exercise, as defined by having presented for a baseline clinical exam and reported slight or moderate activities in a 24-hour period. **Exclusion criteria:** Prevalent dementia. Poor cognitive function whose dementia status could not be confirmed. Prevalent	**Risk factor/exposure 1:** Physical activity, specifically walking **Method of assessing risk factor/exposure 1:** Self report. "Participants were asked about the average amount of distance walked per day." Other--Physical Activity Index (referenced in paper, but not described, other than saying it is a common measure of daily metabolic output). Also assessed physical function at baseline via battery of test, for a "physical performance score." **Covariates/potential confounders adjusted for in analyses:** Age; APOE; Baseline CASI; Declines in activity since mid adulthood **Method(s) of**	**1) Follow-up rate:** 2257 out of 3734 (60.4%). Initial Honolulu Heart Program had 8006 men. 3734 of survivors initially potentially eligible for this study. Excluded from f/u: men who died (n=377), prevalent dementia (n=145), poor cognitive function (n=75) whose dementia status couldn't be confirmed, Parkinsons (n=39), prevalent stroke (n=116), missing data on physical activity (n=194), failed to present for a clinic visit (n=112), no slight or moderate activity (n=76), smokers (n=161), use of walker or cane (n=27). **2) Important baseline differences:** NA **3) Outcome of interest #1** Incidence of dementia: 158 (15.6/1000 person-years). Among these, 101 (10.0/1000 person-yrs) were attributed to AD and 30 (3.0/1000 p-y) attributed to vascular dementia as sole or primary cause. 27 cases (2.7/1000 prs-yrs) with mixed AD and other dementia. Median time from baseline exam to Dx was 4.7 yrs (range: 2.4-7.4). **4) Outcome of interest #2--Dementia** Men who walked the least (<0.25 mile/d) experienced a 1.8 fold excess of total dementia compared to those	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		Parkinson's disease or stroke. Subjects with missing data on physical activity. Continued employment. Daily activities failed to meet criteria for being slight or moderate. Smokers. Use of walker or cane.	**assessing cognitive status:** Initial screening with CASI <74. 3 screening phases. NINCDS-ADRDA DSM IIIR Other: Informant Questionnaire on Cognitive Decline in the Elderly **Informant interview?:** Yes	who walked the most (> 2 mile/d). Compared with men who walked the most (> 2 mile/d), an excess of dementia was observed in those who walked 0.25 to 1 mile/d (17.6 vs. 10.3/1000 person-yrs; RH, 1.71; 95% CI, 1.02-2.86). (RH = relative hazard) After adjusting for covariates, a 1.9-fold excess risk of total dementia was found in me who walked less than 0.25 mile/d compared to those who walked > 2 mile/d (RH, 1.93; 95% CI, 1.11-3.34). Compared with the most active men, those who walked 0.25 to 1 mile/d experienced a 1.7-fold excess in dementia risk (RH, 1.75; 95% CI, 1.03-2.99). **5) Outcome of interest #3—Alzheimer's Disease** There was an 1.8-fold excess of AD in men who walked 2 mile/d or less vs. those who walked more than 2 mile/d. An association between walking and vascular dementia was less apparent. After adjusting for covariates, risk of AD was 2.2-fold higher in men who walked the most (RH, 2.21; 95% CI, 1.06-4.57). **6) Outcome of interest #4—Timed walk** "The focus of this report is on day-to-day activity; however, a faster timed walk at baseline eval was also	

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				associated with a decreased age-adjusted incidence of dementia."	
ADAPT Research Group, 2007	**Geographical location:** Baltimore, MD Boston, MA Rochester, NY Seattle, WA Sun City, AZ Tampa. FL **Setting:** Community **Study design:** RCT **Test intervention:** Celecoxib 200mg BID **OR** Naproxen Sodium 220mg BID **Comparator intervention(s):** Placebo **Number of participants enrolled:** 2528 **Duration of follow up:** ~735 days **Time from risk factor assessment to final cognitive assessment:** RCT with annual	**Age:** Mean (SD): 74 Range: 70-90 **Sex:** [n (%)] Female: 1160 (45.9%) Male: 1368 (54.1%) **Race/ethnicity:** [n (%)] White, non-Hispanic 2452 (97%) African-American 38 (1.5%) Hispanic 18 (0.7%) Other 20 (0.8%) **Baseline cognitive status:** Non-demented For MCI analyses baseline status excluded those with prevalent MCI/PrAD But all have first degree relatives with AD **Inclusion criteria:** ≥ 70 yo; h/o at least 1 first degree relative w/ Alzheimer-like dementia; aspirin use of ≤ 81 mg/day allowed **Exclusion criteria:** Regular use of NSAIDS	**Risk factor/exposure 1:** nsaid **Method of assessing risk factor/exposure 1:** RCT with naproxen, celecoxib, placebo **Covariates/potential confounders adjusted for in analyses:** Randomization stratified by age group, field site **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes	**1) Follow-up rate:** 83-5% follow up but nearly half "terminated drug" **2) Important baseline differences:** p's not given, nothing looks obvious **3) Outcome of interest #1:** Neither tx associated with a decreased risk of AD. **4) Outcome of interest #2:** HR for possible increased risk of AD celecoxib 4.11 (1.3-13), naproxen 3.57 (1.09-11.7)	**Comments:** Study terminated bec of cox II. Almost half of subjects "terminated" drug **Quality assessment:** *For RCTs:* 1) Baseline comparability?: Yes 2) Valid AD/cognitive outcomes assessment?: Yes 3) Subjects/providers blind?: Yes 4) Outcome assessors blind?: Partial 5) Incomplete data adequately addressed?: No 6) Differential dropout rate < 10%?:Yes 7) Overall dropout rate < 30%?: No 8) Conflict of interest reported and insignificant?: Yes 9) Randomization adequate?: Yes 10) Allocation concealment adequate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	cognitive screening Time varied because of termination of trial – 75th percentile ~830 days				
Aggarwal, Bienas, Bennett, et al., 2006 CHAP Study	**Geographical location:** 3 southside Chicago neighborhoods (Morgan Park, Washington Heights, & Beverly) **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 6158 **Duration of follow up:** mean 4.1 (range 0.4 – 6.9) **Time from risk factor assessment to final cognitive assessment:** mean 4.1 (range 0.4 – 6.9)	**Age:** Mean (SD): 73.1 Range: ≥65 **Sex:** [n (%)] Female: 61.9% Male: 38.1% **Race/ethnicity:** [n (%)] AA 49.8% Other 50.2% **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 yo; institutionalized residents included **Exclusion criteria:** NR	**Risk factor/exposure 1:** Smoking **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Freq participation in cog act. APOE Time from baseline to cog eval **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** No	**1) Follow-up rate:** 1064/1527 (69.7%) **2) Important baseline differences:** NR **3) Outcome of interest #1:** Current smokers at greater risk of AD than never smokers Former smokers not at greater risk of AD than non-smokers (Ever smoked vs never smoke did not show increased risk of AD for smoking) **4) Outcome of interest #2** Current smokers, no e4 – increased risk of AD Former smoker, e4 – reduced risk of AD **5) Outcome of interest #3** Current smokers, pack yrs did not assoc with risk Former smokers, as pack years increased, AD risk decreased	**Comments:** For Q1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Can't Tell 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial 7) Outcome assessment blind to exposure?: Can't tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Can't tell 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Akbaraly, Hininger-Favier, Carriere, et al., 2007 EVA Study	**Geographical location:** Nantes district, France **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 702 completed 9 waves of data collection (Numbers vary by analyses, but this seems to be the maximum in any analyses). **Duration of follow up:** 9 yrs **Time from risk factor assessment to final cognitive assessment:** 9 yrs from baseline, but risk factor collected each wave also. Analyses looked at parallel change in risk factor level and cognitive performance	**Age:** Mean (SD): 65 (3.0) yrs **Sex:** [n (%)] Female: 436 (62.1) Male: 266 (37.9) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented – this is not stated but is assumed. Only those that were followed for 9 yrs were included in the analyses, so it is likely that anyone demented at baseline would have been able to still do the cognitive tests 9 yrs later. **Inclusion criteria:** Born between 1922-1932 Living in Nantes district of France Recruited from electoral rolls and information campaigns When ind enrolled automatically asked spouse to participate. **Exclusion criteria:** None	**Risk factor/exposure 1:** selenium **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Sex Educational level Time period of observation Baseline plasma selenium level Diabetes Hypertension Dyslipidemia Hx of cardiovascular disease **Method(s) of assessing cognitive status:** Other – cognitive decline on multiple measures using both continuous change as outcome and dichotomous outcomes using two cutoffs (25th and 10th percentiles of change) The analytical approach(mixed models) takes into	**1) Follow-up rate:** 702/1288 (denominator excludes those who did not complete fup due to death) **2) Important baseline differences:** NR reported by exposure group **3) Outcome of interest #1** 9-yr change in selenium was associated with 9 yr continuous change in MMSE only (CI=0.12-0.62). It was not significant for other cognitive measures. **4) Outcome of interest #2** Change in selenium during the 1st 2 years of the study was not associated with cognitive change in years 1-9 of the study **5) Outcome of interest #3** Using the categorical cognitive decline measure, cognitive decline at either the 25th or the 10th percentile was significant for MMSE, DSS, TMTB (but not at both cut points). Only FTT was significant at both impairment cut points.	**Comments:** Question 2 Did not covary for age at baseline because it was not sig associated with change in cognition **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial, recruited from electoral rolls and advertisement 2) Selection minimizes baseline differences in prognostic factors?: Partial 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't tell, but probably yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			account the baseline score **Informant interview?:** No		
Akbaraly, Portet, Fustinoni, et al., 2009 3 City Study	**Geographical location:** Dijon (n=4931) Montpelier (n=2259) France **Setting:** Community 1999-2001 **Study design:** Prospective cohort **Number of participants enrolled:** 5692 **Duration of follow up:** 4 yr **Time from risk factor assessment to final cognitive assessment:** 4 yr	**Age:** Mean (SD): 73.7(SDNR) Range: ≥65 **Sex:** [n (%)] Female: 3468 (60.9%) Male: 2238 (39.1%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 Had both F/U appts leisure activity Ques Complete baseline information **Exclusion criteria:** dementia	**Risk factor/exposure 1:** 16 leisure activities at baseline, categorized as stimulating, passive, physical or social and analyzed by tertiles **Method of assessing risk factor/exposure 1:** 2 Self-report Ques. Daily with 3 pt scale Monthly with 4 pt scale **Covariates/potential confounders adjusted for in analyses:** Age Sex Study center (Dijon or Montpelier) Marital status Educational level Occupational grade Health status – Vascular risk factors Diabetes HTN High cholesterol Hx of CVD Depressive sx CES-D > 16	**1) Follow-up rate:** 92.3% of cohort had F/U data This was a retrospective analysis of prospectively collected data **2) Important baseline differences:** Participants varied on numerous socio-demographic and clinical factors across the tertiles of leisure activities **3) Outcome of interest #1** All cause dementia over time (161 new cases over 4 y) Stimulating activities related to reduced risk: HR = 0.46, CI=0.27/0.80; independent of other proxies for CR, vascular disease risk factors, and other leisure activities BUT if control for cognitive impairment at baseline as well as health status, CI includes one and association is now a trend **4) Outcome of interest #2** Alzheimer's Disease over time (105 new cases over 4 y) Stimulating activities related to reduced risk: HR = 0.50, CI=0.33/0.78; independent of other proxies for Cognitive Reserve, vascular disease risk factors, and other leisure activities	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Partial, didn't include baseline MCI differences until last analysis 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Partial, race not given 5) Validated method for ascertaining exposure?: No, scales not validated; 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes, 11) Analytic methods appropriate?: Partial – association between leisure activity and risk of dementia over time was tested by proportional hazards model

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Physical fx AODL (score > 0) Cognitive impairment MMSE (score <24) APOE genotype **Method(s) of assessing cognitive status:** 3-step process: Neuropsych tests Individual assessment Committee review using NINCDS-ADRDA And DSM-IV criteria **Informant interview?:** No	BUT if control for cognitive impairment at baseline as well as health status, CI includes one and association becomes trend **5) Outcome of interest #3** In the most adjusted model, the HR for AD by tertile was: Stimulating leisure activities High: 0.39 (0.21-0.71) Mild: 0.45 (0.26-0.77) Ref Passive leisure activities: High: 0.68 (0.41-1.13) Mild: 1.02 (0.62-1.69) Ref Physical leisure activities: High: 1.29 (0.80-2.09) Mild: 0.87 (0.50-1.51) Ref Social leisure activities: High: 0.70 (0.41-1.21) Mild: 1.06 (0.67-1.68) Ref In a sensitivity analysis excluding those with low MMSE at baseline, then those with incident AD at 1st follow-up, then those with MCI at baseline, stimulating leisure activities remained associated with a lower risk of AD	(time scale was age and entry point). Interactions were tested BUT poor measurement of risk was further compounded by making scale into tertiles simply because distribution of results was non-normal. Non-normal distribution of some of the activities would be expected. Were outliers tested? Was data examined as continuous variable with and without outliers and compared to see if results the same? Not done or data not shown.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Akomolafe, Beiser, Meigs, et al., 2006 Framingham Study	**Geographical location:** Framingham, Massachusetts, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2210 **Duration of follow up:** 12.7 years **Time from risk factor assessment to final cognitive assessment:** Varies. Diabetes was assessed at each of the biennial exams.	**Age:** Mean (SD): 70 years (7.0) **Sex:** [n (%)] Female: 1325 (60%) Male: 885 (40%) **Race/ethnicity:** NR **Baseline cognitive status:** Normal Non-demented **Inclusion criteria:** Participants in the Framingham study Not demented **Exclusion criteria:** MCI or dx as having dementia	**Risk factor/exposure 1:** Diabetes mellitus **Method of assessing risk factor/exposure 1:** Self-report Direct measurement Medical record **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status Total homocysteine Smoking Alcohol BP Cardiovascular risk factors Stroke **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?** Can't tell	**1) Follow-up rate:** 2210/2611= 84.6% **2) Important baseline differences:** DM>control Male Sex, systolic BP, BMI, stroke, other cardiovascular risk factors Control>DM Education >12 years, <2 alcoholic drinks/day **3) Outcome of interest #1** 17 of 202 persons with DM (8.4%) and 220of 2008 persons without DM (11.0%) developed AD RR 1.15 (95% confidence interval, 0.65-2.05). **4) Outcome of interest #2** Among subjects without an apolipoprotein E □4 allele or elevated plasma homocysteine levels, 44 of 684 persons (6.4%) developed AD. RR diabetics with nondiabetics 2.98 (95% confidence interval, 1.06-8.39; *P*=.03). Age >75 years and DM RR incident AD 4.77 (95% confidence interval, 1.28-17.72; *P*=.02).	**Comments:** Results may be effected by baseline differences in other risk factors that could be associated with AD **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Alvarado, Zunzuneg	**Geographical location:**	**Age:** Range:65-89 yrs old	**Risk factor/exposure 1:**	**1) Follow-up rate:** 557/964 = 57.7%	**Comments:** None

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
ui, Del Ser, et al., 2002 Aging in Leganes Study	Leganes, Spain **Setting:** Community **Study design** Prospective cohort **Number of participants enrolled:** 964 enrolled 557 completed follow up **Duration of follow up:** 4 years **Time from risk factor assessment to final cognitive assessment:** 4 years	**Sex:** Female: 294(52.7%) Male: 263(47.3%) **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** At least 65 yrs old, living at home, without severe cognitive impairment or visual impairment, low educational level (without primary school completion) **Exclusion criteria:** Severe cognitive deficit (92 subjects excluded) Visual impairment (unable to see 23-point characters)(102 subjects excluded)	educational attainment **Method of assessing risk factor/exposure 1:** Self-report 1) illiterate 2) literate (no formal educ, can read and write) 3) 1-3 yrs of formal education 4) 4 or more years of formal education Then reclassified into 2 categories: 1) incomplete primary school 2) complete primary school **Risk factor/exposure 2:** occupation **Method of assessing risk factor/exposure 2:** Self-report Lifelong occupation, according to the Spanish National Classification of Occupations 5 categories: 1) white collar and skilled workers 2) semiskilled	**2) Important baseline differences:** NA **3) Outcome of interest #1** 557 subjects completed follow up. Total 176 subjects combined experienced decline: 61 subjects (11%) experienced severe decline (> 1 SD below mean, -8 to-23/32) 115(20.6%) experienced mild decline.(change within 1SD below mean, -2 to-7/32) Less than primary education vs complete primary risk of cognitive decline: OR 1.49(95%CI:0.92-2.43) Less than primary and farm worker vs complete primary and non-farm worker: OR 2.36(95%CI 1.16-4.81) Less than primary and non-farm worker vs complete primary and non-farm worker: OR 1.39(95% CI: 0.85-2.29) Farm workers vs non-farm workers: OR 1.79 (95% CI:0.99-3.23) **4) Outcome of interest #2** Authors' conclusion: "the association of low education level with cognitive decline is supported by our study" among a Spanish population with low levels of formal education	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Yes for education, Can't Tell for occupation 6) Validated method for ascertaining clinical outcomes?: Yes (authors state the method has been validated) 7) Outcome assessment blind to exposure?: No 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No. attrition exceeded 30% 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			3) unskilled 4) housewives 5) farm workers Reclassified to: 1) farm workers 2) others **Method of assessing risk factor/exposure 3:** Combined education and occupation. 1) primary school and not farm workers 2) no primary school and farm workers 3) no primary school and not farm workers **Method(s) of assessing cognitive status:** "Cognitive function assessed via items involving orientation and memory that have been validated for people with low levels of education." Total cumulative score (range 0-32) at baseline and 4-yr f/u. Both continuous and change scores in 3 categories: 1) "mild decline" = -2 to -7		

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			2) "severe decline" -8 to -23 2) "normal" = -1 to 12 **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status Occupation **Method(s) of assessing cognitive status:** Other – Cognitive decline over 4 years. Short Portable Mental Status Questionnaire (SPMSQ) **Informant interview?:** No		
Alves de Moraes, Szklo, Knopman, et al., 2002 ARIC Study	**Geographical location:** Forsyth County, NC Jackson, MS Minneapolis, MN Washington County, MD **Setting:** Community **Study design:**	**Age:** Mean (SD): 56.7 (5.6) **Sex:** Female: 51.7% Male: 48.3% **Race/ethnicity:** White 6342 (78.7%) Other: 1716 (21.3%) **Baseline cognitive**	**Risk factor/exposure 1:** htn **Method of assessing risk factor/exposure 1:** Self-report Direct measurement htn defined by self report, use of antihypertensive meds,	**1) Follow-up rate:** 11320/15782 (72%) had both follow up visits. Final n of 8058 by excluding those with strokes, tias, missing cognitive scores, or cns meds **2) Important baseline differences:** I see baseline differences between those who followed up and those who didn't but not between those with and without htn.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Prospective cohort **Number of participants enrolled:** 8058 **Duration of follow up:** 6 years **Time from risk factor assessment to final cognitive assessment:** risk factor assessment done at beginning and end of six year period. Cognitive testing also at both visits.	**status:** Subjects don't appear to have been screened on the basis of cognitive functioning. **Inclusion criteria:** Participating in ARIC Study (Atherosclerosis Risk in Communities) **Exclusion criteria:** History of stroke or transient ischemic attack in visit 2 and/or visit 4 Taking medications that may affect the central nervous system Missing cognitive test scores in either visit	or sbp $\geq$140 or dbp $\geq$ 90. Four categories: nl bp, incident htn, partially controlled htn (one or other visits had nol bps) and uncontrolled htn. **Covariates/potential confounders adjusted for in analyses:** Age, Race, Sex, Educational level, diabetes **Method(s) of assessing cognitive status:** change in test score **Informant interview?:** No	**3) Outcome of interest #1** In comparing each category of htn to normotensive subjects, the only significant difference was that between uncontrolled hypertensives and normotensives for the DSS score. In data not shown this is limited to inidividuals over the median age of the cohort (>56 yrs at the first visit considered here).	4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Andel, Crowe, Pedersen, et al., 2008 The HARMONY Study Swedish Twin Registry	**Geographical location:** Sweden **Setting:** Community **Study design:** Case-control design and co-twin control design "Prospective case-control" (i.e., participants in a case-control study in 1967	**Age:** Mean (SD): 48.1 (4.9) at baseline and 79.5 (5.0) at f/u. **Sex:** Female: 61% Male: 39% **Race/ethnicity:** NR **Baseline cognitive status:** Normal Demented	**Risk factor/exposure 1:** Light exercise or hard physical training at midlife **Method of assessing risk factor/exposure 1:** Self-report: "How much exercise have you had from age 25 to 50?" 0=hardly any 1=light exercise 2=regular exercise 3=hard physical	**1) Follow-up rate:** 3134/4506 = 70%. 3366 participated in telephone screening and/or clinical w/u for dementia. 1372 drop outs (who were 1.5 yrs older, more women, fewer high education level, less likely to drink alchohol). Some differences in exercise levels also. **2) Important baseline differences:** Cases were older than controls, but the groups did not differ in time of	**Comments:** Method of assess cognitive status not reported. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	follow-up in 1998) **Number of participants enrolled:** 4506 were eligible to be contacted by HARMONY in 1998. 3366 participated in telephone screening and/or w/u for dementia. 3134 in final analysis (includes 655 twin pairs). 70% response rate. **Duration of follow up:** 31 years **Time from risk factor assessment to final cognitive assessment:** 31 years	**Inclusion criteria:** All living twins in the STR cohorts of twin pairs who completed a questionnaire in 1967 or 1970 and who underwent dementia assessment in 1998 or later as part of the HARMONY study. HARMONY inclusion criteria include all twins in the STR who were living and 65 years or older in 1998. Controls were selected from the community (including persons in long-term care). **Exclusion criteria:** NR	training **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Other—diet, BMI, alcohol, smoking, angina. Also explored lifestyle as a possible effect modifier **Method(s) of assessing cognitive status:** Two-stages: screen followed by clinical evaluation. "Telephone screening and/or clinical work-up for dementia." **Informant interview?** Yes	follow-up. **3) Outcome of interest #1** Of 3134, 264 had dementia (176 with AD). **4) Outcome of interest #2** Case-control analysis Crude OR (95% CI), with hardly any exercise as the reference: Dementia light exercise: 0.61 (0.44-.086) regular exercise: 0.21 (0.10-0.45) hard training: 0.78 (0.46-1.30) AD light exercise: 0.62 (0.41-0.93) regular exercise 0.21 (0.09-0.52) hard training: 0.78 (0.46-1.30) No effect modifiers for lifestyle factors were identified. Adjusted OR (95% CI), with hardly any exercise as the reference: Dementia light exercise: 0.63 (0.43-0.91) regular exercise: 0.34 (0.16-0.72) hard training: 0.70 (0.40-1.24) AD light exercise: 0.64 (0.41-1.00) regular exercise 0.34 (0.14-0.86) hard training: 0.65 (0.33-1.29) **5) Outcome of interest #3** Co-twin control analysis "There was a statistical trend indicating that twins who exercised	ascertaining exposure?: No 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				more than their co-twins had reduced odds of dementia in analyses with and without controlling for education." Adjusted OR for co-twin controls association between exercise and dementia: 0.66 (95% CI: 0.24-1.83)	
Anonymous, 2002 The Heart Protection Study	**Geographical location:** 69 UK sites **Setting:** Clinical – Special, hospital based study clinics **Study design:** RCT; 2*2 factorial **Test intervention:** Simvastatin 40mg daily; antioxidant vitamins **Comparator intervention(s):** Placebo **Number of participants enrolled:** 20,536 (10,269 intervention; 10, 267 placebo) **Duration of follow up:** Mean= 5 years **Time from risk factor**	**Age:** Range:~40 – 80 years **Sex:** [n (%)] Female: 5082 (24.7%) Male: 15454 (75.3%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented (no existing diagnosis at baseline; no screening or formal assessment done) **Inclusion criteria:** Age about 40-80 Total cholesterol >= 135 mg/dl High risk for death from CHD **Exclusion criteria:** GP determined statin is clearly indicated Chronic liver or renal disease severe CHF	**Risk factor/exposure 1:** statin **Method of assessing risk factor 1:** Direct measurement-calendar packed tablets **Method(s) of assessing cognitive status:** 1. modified Telephone interview for cognitive status at final follow-up only 2. Dementia – assessment method not specified but appears to be non-study clinician diagnosis **Informant interview?:** No	**1) Follow up rate:** >99% m-TICS score <22/39 at final follow-up: 23.7% simvastatin vs. 24.2% placebo; p=ns Mean m-TICS at final follow-up (unadjusted): 24.08 simvastatin vs. 24.06 placebo; difference between group means = 0.02 [SE 0.07] Incident dementia (dementia/total): 31/10,269 (0.3%) simvastatin vs. 31/ 10267(0.3%) placebo (no p value)	**Comments:** Poor measures of cognitive change (TICS may not be sensitive to change) Poor assessment for dementia **Quality assessment:** *For RCTs:* 1) Baseline comparability? Partial 2) Valid AD/cognitive outcomes assessment? No 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes for TICS, uncertain for dementia 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment to final cognitive assessment: Mean = 5 years	inflammatory muscle disease conditions limiting adherence (e.g. dementia or psychiatric disorder)			
Applegate, Pressel, Wittes, et al., 1994 SHEP study	**Geographical location:** USA, Multicenter **Setting:** Community **Study design:** RCT – double-blind, placebo controlled **Test intervention:** Chlorthalidone 12.5 or 25mg daily, step 1 – atenolol 25 or 50m mg or reserpine 0.05 or 0.10 mg daily **Comparator intervention(s):** Matching placebo **Number of participants enrolled:** 4736 in sample overall; 1993 had detailed cognitive assessment (987 intervention, 1006 control) **Duration of follow up:** Mean 5 years	**Age:** Mean (SD): 71.6 (6.7) **Sex:** [n (%)] Female: 807 (57%) Male: 566 (43%) **Race/ethnicity:** [n (%)] White non-Hispanic (79.2%) Black 13.85 Hispanic 1.8% Asian 4.3% Other 0.9% **Baseline cognitive status:** Non-demented **Inclusion criteria:** Mean SBP 160-219 and DBP <90 mmHg **Exclusion criteria:** History or signs of major CV disease likely to require pharmacologic and other treatment; other major diseases (e.g., cancer) with competing risk factors for primary endpoint; h/o	**Covariates/potential confounders adjusted for in analyses:** None **Method(s) of assessing cognitive status:** Other – Short care cognitive assessment; Digit symbol substitution; addition test; findings A's test; Boston Naming Test; Letter Sets Test; Delayed Recognition Span Test **Informant interview?:** No	**1) Follow-up rate:** 1564/1993 **2) Important baseline differences:** None **3) Outcome of interest #1** Mean short care cognitive impairment assessment (placebo change minus intervention change) = 0.05 (95% CI -0.0006 – 0.11); intervention declined more but not statistically significant **4) Outcome of interest #2** "There were no significant differences in the mean changes between treatment and control groups for any of the cognitive function tests" (data not given) **5) Outcome of interest #3** Dementia: 37/2365 in intervention group; 44/2371 in control group; OR 0.84 (0.54-1.31) Adverse effect leading to drug discontinuation: intervention group 665/2365, control group 493/2371; OR 1.49 (1.30-1.70)	**Comments:** None **Quality assessment:** *For RCTs:* 1) Baseline comparability?: Yes 2) Valid AD/cognitive outcomes assessment?: Yes 3) Subjects/providers blind?: Yes 4) Outcome assessors blind?: Yes 5) Incomplete data adequately addressed?: Partial 6) Differential dropout rate < 10%?:Yes 7) Overall dropout rate < 30%?:Yes 8) Conflict of interest reported and insignificant?: Can't Tell 9) Randomization adequate?: Yes 10) Allocation concealment adequate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Time from risk factor assessment to final cognitive assessment: 5 years	dementia, alcohol abuse			
Arvanitakis, Grodstein, Bienias, et al., 2008 Religious Orders Study	**Geographical location:** Numerous US locations **Setting:** Community –Religious orders **Study design:** Prospective cohort **Number of participants enrolled:** 1019 **Duration of follow up:** annual follow up from one to 12 years **Time from risk factor assessment to final cognitive assessment:** Variable because risk factor info collected at each annual assessment. Time between risk factor and final outcome could be between 1 and 12 years follow-up	**Age:** Mean: 75 yo **Sex:** [n (%)] Female: 707 (69.4%) Male: 312 (30.6%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Enrolled in Religious Order Study; agree to annual clinical evaluations & brain donation upon death **Exclusion criteria:** Dementia at baseline	**Risk factor/exposure 1:** nsaids/asa **Method of assessing risk factor/exposure 1:** inspection of pill bottles at each assessment **Covariates/potential confounders adjusted for in analyses:** Age Sex Education, vasc risk factors, E4 **Method(s) of assessing cognitive status:** NINCDS-ADRDA Other: cognitive change on multiple tests **Informant interview?:** No	**1) Follow-up rate:** 1019/1102 had at least one annual follow-up assessment **2) Important baseline differences:** nsaid users, more women, higher sbp. ASA users: older, to be male, more mi's, more cva's **3) Outcome of interest #1** Risk of AD not different according to use of nsaid or asa baseline. **4) Outcome of interest #2** nsaids vs not AD 1.19 (0.87-1.62) **5) Outcome of interest #3** ASA vs not AD 0.84 (0.63-1.11) 6) Outcome of interest #4 Cognitive decline on multiple measures was not associated with use of NSAIDS or ASA (p values ranged from 0.14 to 0.77)	**Comments:** Highly educated sample **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Arvanitakis, Schneider, Wilson, et al., 2008 Religious Orders Study	**Geographical location:** Multiple US sites **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1011 929 with ≥ 1 yr f/u analyzed **Duration of follow up:** 1 – 12 yrs (mean NR) **Time from risk factor assessment to final cognitive assessment:** 1 – 12 yrs	**Age:** Mean (SD): Group A 72.7 (6.1) Group B 75.2 (7.1) **Sex:** Female: 638 (69%) Male: 291 (31%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Normal Non-demented **Inclusion criteria:** "Older Catholic Clergy" **Exclusion criteria:** Dementia	**Risk factor/exposure 1:** Statin simvistatin 32 lovastatin 33 atorvastatin 35 pravastatin 12 fluvastatin 5 antidiabetic agents **Method of assessing risk factor/exposure 1:** Other – medication containers inspected **Risk factor/exposure 2:** Vascular disease summary score (MI, CHF, claudication, stroke) Vascular risk factor summary score (HTN, diabetes, smoking) **Method of assessing risk factor/exposure 2:** Self-report Other – clinical exam for stroke **Covariates/potential confounders adjusted for in analyses:** Age	**1) Follow-up rate:** 929 of 1011 (91.8%) HR for AD = 0.91 (95% CI 0.54 to 1.52), adjusted for age, sex, education, Analysis that added vascular disease score and vascular risk factor score "did not change this finding" Interaction effects were non-significant for : statins and vascular diseases or risk factors or ApoE e4 Continuous outcome: Statin use associated with change in cognition adjusted for age, sex and education. Regression coefficient, (Standard error), p value Global cognition: -0.014, (0.012,) p=0.245 Episodic memory: -0.017, (0.016), p=0.290 Semantic memory: -0.008, (0.013), p=0.529 Working memory: -0.009, (0.009), p=0.321 Perceptual speed: -0.006 (0.013), p=0.617 Visuospatial ability: -0.009, (0.010), p=0.329 (unsure when f/u assessment was performed) Continuous outcome [see instructions above]	**Comments:** F/U time is not specified for change in cognition (AD outcomes appear appropriately analyzed, cognitive change may not be); only baseline statin use evaluated **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Race Sex Educational level In a separate model, they also added vascular risk factors and stroke as covariates. **Method(s) of assessing cognitive status:** NINCDS-ADRDA Other – change in performance on cognitive tests over time **Informant interview?:** No		
Atti, Palmer, Volpato, et al., 2008 Kungsholmen Project	**Geographical location:** Kungsholmen area of Stockholm, Sweden **Setting:** Community **Study design** Prospective cohort **Number of participants enrolled:** 1255 **Duration of follow up:** 9 years **Time from risk factor**	**Age:** Mean (SD): 80.8 (4.5) **Sex:** [n (%)] Female: 925 (73.71%) Male: 330 (26.29) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Normal Non-demented **Inclusion criteria:** All residents of the Kungsholmen area	**Risk factor/exposure 1:** Obesity **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status Depressive symptoms	**1) Follow-up rate:** 646/1255 *100= 51.47% of those not in the follow-up sample 291 subjects were deceased at follow-up and 189 had incident dementia. Only 170 dropped out and 98 lacked BMI measurement. **2) Important baseline differences:** The sample had more women More women were underweight More men had chronic disease at baseline. **3)Outcome of interest #1** Overweight subjects (n575, 22.5%) had a lower risk of developing AD over 9 years of follow-up (HR50.66, 95% CI50.50–0.88), which	**Comments:** The participants of this study are older than some of the other studies in the geriatric populations with a mean age of 80.8. Though analysis for AD alone was done, unsure as to what proportion of dementia was specifically due to AD. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment to final cognitive assessment: 9 years	**Exclusion criteria:** Diagnosis of dementia; Unknown educational level, Baseline MMSE score less than 20, Very old age (≥95)	Impairment in ADLs Chronic disease at baseline. **Method(s) of assessing cognitive status:** DSM III (agreement among 3 physicians. If they disagree, patient examined by third) **Informant interview?:** No	was confirmed when only incident cases occurring between 6 and 9 years were considered (n 521, 15.3%; HR50.67, 95% CI50.40–1.15) **4) Outcome of interest #2** (The following include all types of dementia) Risk of Developing Dementia at Different Follow-Up Times (Risk Periods) According to Baseline Body Mass Index (BMI) after adjusting for sex, age, education, baseline Mini-Mental State Examination score, depressive symptoms, chronic disease up to baseline, and impairment in activities of daily living **Obesity as a continuous variable:** HR 0.96 (0.92-1.01) (incident dementia between years 3 and 9 of follow up) HR 0.98 (0.94-1.00) (incident dementia between years 1 and 9 of follow up) HR 0.97 (0.91-1.04) (incident dementia between years 6 and 9 of follow up) Categorical, n (%) HR (95% CI) for dementia between years 3 and 9 of follow up In BMI < 20.0 (underweight) 26 (30.9) 0.91 (0.59–1.40) In BMI 20.0–24.9 (normal weight) 115 (31.7) 1 (reference) And in BMI ≥25.0	cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				(overweight/obese) 55 (23.6) 0.72 (0.52–1.02	

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Ball, Berch, Helmers, et al., 2002 ACTIVE Trial	**Geographical location:** 6 metropolitan areas USA **Setting:** Community, Clinical – hospital and clinics, Other – senior housing **Study design:** RCT **Test intervention:** 3 different groups: -Training memory -Reasoning training -Speed processing training A subgroup of each had a booster at 11 months **Comparator intervention(s):** No contact group **Number of participants enrolled:** 2832, of this 2802 analyzed (30 excluded due to inappropriate randomization). **Duration of follow up:** 2 years **Time from risk factor**	**Age:** Mean (SD): 73.6 (5.9) Range: 65-94 **Sex:** [n (%)] Female: 2127 (75.9%) Male: 675 (24.1%) **Race/ethnicity:** [n (%)] White: 2054 (73.3%) AA: 729 (26.0%) Other: 19 (0.7%) **Baseline cognitive status:** Non-demented MMSE above 22. Mean MMSE 27.3 (SD 2.0) (range 23-30) **Inclusion criteria:** Independent living Older than 65 Able to perform ADLs independently At risk for cognitve decline but without it yet. **Exclusion criteria:** -Younger 65y -MMSE lower 22 -Self report AD dx. -Substantial functional decline -Medical condition that could predispose to severe functional decline or death.	**Covariates/potential confounders adjusted for in analyses:** Age, Sex, Educational level, Baseline cognitive status (they state this was done with overall pattern of results being similar but data not shown) **Method(s) of assessing cognitive status:** Other – specific to each of the interventions (see bove for each intervention measurement). Measures completed at: baseline, Immediate post test, first annual and second annual **Memory composite**: Hopkins verbal learning test, auditory verbal learning verbal test, Rivermead Behavioral Memory test. **Reasoning composite:** Word series, Letter series, letter sets.	**1) Follow-up rate:** 2802 included in analysis. (at 2 year follow up a total of 2244 assessed (80%), drop outs due to death, protocol violations, withdrawal due to scheduling, illness or lack of interest in continuing). **2) Important baseline differences:** Randomized group was Slightly younger(mean 74 vs 75), more educated (13.5 vs 12.3 years), higher MMSE scores (27.3 vs 26.8) and fewer non white (27 vs 40%). This is in comparison with non randomized group (refused participation) there is no actual description of baseline characteristics or differences among intervention groups vs. control! **3) Outcome of interest #1** Every day problem solving at 2 years: Effect size compared to control: Memory training (-0.073), Reasoning training (-0.027), Speed training (0.031); p=ns for all Proportion showing improvement at 2 years (>1 SEM above baseline): Memory training (21%), Reasoning training (25%), Speed training (26%), control (23%) **4) Outcome of interest #2** ADL and IADL functioning. Proportion showing improvement at 2 years (>1 SEM above baseline): Memory training (17%), Reasoning	**Comments:** Question 5 60% of the participants in each group where given boosters at 11 months and this data was analyzed separately. *For RCTs:* 1) Baseline comparability?: Can't Tell 2) Valid AD/cognitive outcomes assessment?: Yes 3) Subjects/providers blind?: No 4) Outcome assessors blind?: Yes 5) Incomplete data adequately addressed?: Yes Differential dropout rate < 10%?:Yes 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%?: Yes 8) Conflict of interest reported and insignificant?: No, first author has part ownership of company that makes the proximate test for speed of processing. 9) Randomization adequate?: Yes 10) Allocation concealment adequate?: Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment to final cognitive assessment: 2 annual post test (2 years)	- Severe loss of vision (20/70), hearing or communication abilities. - Prior participation in cognitive trials (recent cognitive training). Planning to move out of the area	**Speed of processing** Useful field of view tasks 2-4.. **Informant interview?:** No	training (16%), Speed training (17%), control (17%) **5) Outcome of interest #3** Everyday speed post test Proportion showing improvement at 2 years (>1 SEM above baseline): Memory training (33%), Reasoning training (29%), Speed training (30%), control (29%) **6) Outcome of interest #4** Driving habits Proportion showing improvement at 2 years (>1 SEM above baseline): Memory training (16%), Reasoning training (16%), Speed training (16%), control (18%) For the 4 primary outcomes assessed in each of the intervention groups, the effects were generally small (most below 0.10) and did not differe significantly in both assessments at 1 year or 2 years after intervention. Therefore no training effects on everyday function where detected at 2 years. Measurement of proximal outcome composites was performed (this is not their primary outcomes) Here they measured memory, reasoning and speed as outlined in previous column. Each intervention improved the targeted cognitive ability compared with baseline, durable to 2 years ($p < .001$ for all). Booster sessions enhanced training gains significantly in reasoning and	

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				speed (p.001) but not for memory.	
Barnes, Alexopoulos, Lopez, et al. 2006 Cardiovascular Health Study	**Geographical location:** 4 US counties (NC, MD, CA, PA) **Setting:** Community **Study designed:** Prospectively **Number of participants enrolled:** 5888 in overall cohort; 2220 in this analysis **Duration of follow up:** 6 years **Time from risk factor assessment to final cognitive assessment:** 6 years from initial assessment.	**Age:** Mean: 74 Range: 64-92 **Sex:** [n (%)] Female: 1310 (59%) Male: 910 (41%) **Race/ethnicity:** [n (%)] African-Amer 200 (9%) Other (predom White) 2020 (91%) **Baseline cognitive status:** Non-demented (3ms>9=0) **Inclusion criteria:** Medicare eligible Live in 4 selected U.S communities Age >=65 Able to respond to questions MRI and 3MS completed **Exclusion criteria:** Institutionalized Cancer treatment Wheelchair bound No baseline lipid or statin use data Dementia 3MS < 90 at baseline	**Risk factor 1** Current Depression CEDS 10-item (0-30) >=8 at baseline **Method of assessing risk factor 1:** [Self-report **Risk factor 2** Antidepressant medication use at baseline **Method of assessing risk factor 2:** Direct measurement-medication bottles **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status Vascular disease **Method(s) of assessing cognitive status:** Other –Clinical and neuropsych testing. MCI = “poor cognitive function that reflected a	**1) Follow-up rate:** CT **2) Important baseline differences:** Depressed subjects were more likely to be female and had higher clinical and subclinical vascular disease **3) Out come of interest #1** MCI Incidence (296 cases) CESD 0-2: Reference CESD 3-7: OR 1.37 (95% CI 1.00 to 1.88) CESD >=8: OR 2.09 (1.46 to 2.97) Stratified analysis by gender, age <=75, race, baseline 3MS, education <12, APOE e4 and antidepressant use did not show significant differences in the odds ratios **4) Outcome of interest #2** Continuous outcome [see instructions above]	**Comment:** High cognitive function at baseline (3MS >=90) **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort)?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can’t Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Can’t Tell 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			decline from prior level" but w/o dementia **Informant interview?:** No		
Barnes, Cauley, Lui, et al., 2007 Study of Osteoporotic Fractures (SOF) Study	**Geographical location:** Baltimore, MD Minneapolis, MN Portland, OR Monongahela Valley, PA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 9704 **Duration of follow up:** Median 10 yrs (range 6-15) **Time from risk factor assessment to final cognitive assessment:** Median 10 yrs (range 6-15)	**Age:** Mean (SD): 71.7 (5.3) Range: 65-99 **Sex:** [n (%)] Female: 9704 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] "primarily white" (>99%) **Baseline cognitive status:** Non-demented *May have included some demented, but unlikely to be many as 1st follow-up assessment was 6 yrs after baseline **Inclusion criteria:** ≥ 65 yo; participating in the Study of Osteoporotic Fractures Study; **Exclusion criteria:** NR	**Risk factor/exposure 1:** smoking **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2:** depression and social networking **Method of assessing risk factor/exposure 2:** gds at year 2 Lubben Social Network Scale at year 2 **Covariates/potential confounders adjusted for in analyses:** Age Educational level Baseline cognitive status Study site **Method(s) of assessing cognitive status:**	**1) Follow-up rate:** over 15 yrs attrition due to causes other than death 832/9704 (9%) Attrition due to death was 4040/9704 (42%) **2) Important baseline differences:** 3 outcome groups differed on almost all baseline characteristics: age, educ, baseline cog score, stroke, DM, HTN, distance walked daily, smoking, ETOH, physical performance, IADL, vision, self-rated health, depressive sxs, social network **3) Outcome of interest #1** Lack of smoking increased likelihood of maintaining cognition **4) Outcome of interest #2** Lack of DM increased likelihood of maintaining cognition **5) Outcome of interest #3** Lack of poor social network increased likelihood of maintaining cognition	**Comments:** 26 pt mmse, 3 groups: no decline in mmse, lowest 33%, use of middle group as a reference **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Other – Cognitive decline in a modified version of the MMSE (26 pts). Grouped as maintain cognition, minor decline, major decline **Informant interview?:** No		
Barnes, Mendes de Leon, Wilson, et al., 2004 Chicago Health and Aging Project	**Geographical location:** Chicago USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 6158 **Duration of follow up:** mean of 5.3 years **Time from risk factor assessment to final cognitive assessment:** 3-6 years	**Age:** Mean (SD): 73.94 (6.46) **Sex:** [n (%)] Female: 3827 (62.2%) Male: 2331 (37.8%) **Race/ethnicity:** [n (%)] African American:3824 (62.1%) White: 2334 (37.9%) **Baseline cognitive status:** Normal Non-demented MCI CIND AAMI AACD (they did not exclude cognitively impaired at baseline) **Inclusion criteria:** Participant in Chicago Health and Aging Project; ≥ 65 yo;	**Risk factor/exposure 1:** Social network **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2:** Social engagement **Method of assessing risk factor/exposure 2:** Self-report (range 0-8) **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Marital status and income	**1) Follow-up rate:** Baseline cohort: 6,102 1,241 died before the first follow-up interview 473 persons were lost to follow-up Of the remaining 4,388 people, 3,899 (88.9%) completed at least one follow-up interview; 3,899 or 6,102 original cohort (63.9%) **2) Important baseline differences:** NR **3) Outcome of interest #1** After controlling for age, sex, race, education, marital status, and income, for each social network there was a 0.002 unit (SE 0.001) reduction in rate of cognitive decline p = 0.001 **4) Outcome of interest #2** Frequency of social engagement was strongly related to rate of cognitive decline, with a reduction of 0.009 unit (SE 0.001) for each point on the social engagement scale.	**Comments:** This article did not exclude patients who had cognitive impairment at baseline. In another paper on the same populations, a third of the sample had MMSEs less than 24 at baseline. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Can't Tell. They did use more than one cognitive test. 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		completed ≥ 1 follow-up **Exclusion criteria:** NR	**Method(s) of assessing cognitive status:** A composite of the MMSE, Immediate and delayed recall of East Boston Story, and Symbol Digit Modalities Test using the average of z scores **Informant interview?:** No	**5) Outcome of interest #3** Results were not affected after the analyses was done after dropping the participants lowest 10 percentile of cognition.	10) Analysis controls for confounding?: Partial. Did not control for baseline cognitive status. 11) Analytic methods appropriate?: Yes.
Bernick, Katz, Smith, et al., 2005 Cardiovascular Health Study (CHS)	**Geographical location:** 4 US Counties (NC, MD, CA, & PA) **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 5880 in overall cohort 3334 for this analysis **Duration of follow up:** Mean of 5.1 years **Time from risk factor assessment to final cognitive assessment:** Mean of 5.1 years from initial assessment	**Age:** Mean (SD): 72.9 (3.6) to 75.9 (5.8) **Sex:** Female: 2014 (60.4%) Male: 1320 (39.6%) **Race/ethnicity:** Non-black 2776 (83.3%) Black 558 (16.7%) **Baseline cognitive status:** Non-demented (3MS>80) **Inclusion criteria:** Medicare eligible; live in 4 selected US communities; ≥ 65 yo; able to respond to questions; underwent study MRI	**Risk factor/exposure 1:** No statin; Intermittent statin (2-4 yrs continuous Tx or 3-5 yrs nonconsecutive use); Continuous statin (>4 yrs continuous Tx) **Method of assessing risk factor/exposure 1:** Direct measurement – medicine bottles **Risk factor/exposure 2:** Age, sex, educational level (self-report), cholesterol, APOE e4 (direct measurement) **Method of assessing risk factor/exposure**	**1) Follow-up rate:** Uncertain Continuous outcome [3MS Baseline values, mean (SD) Continuous (n=293): 93.7 (4.5) Intermittent (n=158): 92.9 (4.6) No treatment (n=2,031): 92.9 (4.9) No treatment (diet recommended, n=501): 92.9 (5.1) No treatment (drug recommended, n=351): 93.1 (4.9) 3MS Unadjusted mean change per year* Continuous (n=293): -0.26 (-0.56 to 0.05) Intermittent (n=158): -0.50 (-0.92 to -0.09) No treatment (n=2,031): -0.75 (-0.86 to -0.63) No treatment (diet recommended, n=501): -0.61 (-0.85 to -0.38) No treatment (drug recommended,	**Comments:** Many excluded due to missing data; did not control for vascular risk factors – but did exclude those with incident TIA/Stroke; N was difficult to assess because had 5880 in overall cohort, then excluded many (legitimately) but other exclusions could have introduced bias (e.g. < 2 yrs f/u cognitive testing, missing lipid data). Time from risk factor assessment also difficult. Initial assessment probably 10 yrs, but assessed repeatedly. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			2: Self-report Direct measurement **Covariates/potential confounders adjusted for in analyses:** age, gender, race APOE e4, cholesterol **Method(s) of assessing cognitive status:** Other – 3MS **Informant interview?:** No	n=351): -0.73 (-1.01 to -0.45) 3MS adjusted mean change per year (age, gender, race APOE e4, cholesterol) Continuous (n=293): -0.27 (-0.61 to 0.06) Intermittent (n=158): -0.45 (-0.89 to -0.01) No treatment (n=2,031): -0.76 (-0.89 to -0.63) No treatment (diet recommended, n=501): -0.61 (-0.87 to -0.36) No treatment (drug recommended, n=351): -0.70 (-1.02 to -0.38) * not specified but should represent f/u – baseline since it is described as a decline	cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Can't Tell 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Berr, Balansard, Arnaud, et al., 2000 EVA Study	**Geographical location:** Nantes district, France **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1389 **Duration of follow up:** 4 yr **Time from risk factor assessment to final cognitive**	**Age:** Mean 65.0 (3.0): **Sex:** Female: 684 (58.7) Male: 482 (41.3) **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented (this is assumed based on the age of the sample. Demented not overtly excluded, but assume few demented at baseline)	**Risk factor/exposure 1:** Selenium **Method of assessing risk factor/exposure 1:** Direct measurement **Risk factor/exposure 2:** carotenoids **Method of assessing risk factor/exposure 2:** Direct measurement **Risk factor/exposure 3:**	**1) Follow-up rate:** 1166/1389 **2) Important baseline differences:** Compared based on TBAR level (not sure how to apply to other risk factors) TBAR > 75th%tile had greater ETOH use, fewer never smoked individuals, higher cholesterol, lower RBC vit E, higher TBAR level **3) Outcome of interest #1** Selenium -<25th %tile vs ≥25%tile OR=1.58 (1.08-2.31) for cog decline **4) Outcome of interest #2** Plasma carotenoids -<25th %tile vs ≥25%tile OR=1.17 (0.75-1.81) for cog decline	**Comments:** Question: Q2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial 2) Selection minimizes baseline differences in prognostic factors?: Partial 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment: 4 yr	**Inclusion criteria:** Born between 1922-1932 Living in Nantes district of France Enrolled from electoral rolls and, to a lesser extent, ad campaigns. When ind enrolled automatically asked spouse to participate. **Exclusion criteria:** None	RBC vit E **Method of assessing risk factor/exposure 3:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status Depressive sxs ETOH and tobacco use BMI Cholesterol triglycerides **Method(s) of assessing cognitive status:** Other – cog decline defined as loss of 3 pts on MMSE – represented worse 15th %tile change **Informant interview?:** No	**5) Outcome of interest #3** RBC Vit E -<25th %tile vs ≥25%tile OR=1.04 (0.68-1.56) for cog decline	exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Beydoun, Kaufman, Satia, et al., 2007 ARIC	**Geographical location:** Four US communities (NC, MS, MN, & MD) **Setting:** Community	**Age:** Mean (SD): No decline: 56.2 (4.2) Decliners:57.7(4.2) **Sex:** [n (%)] Female: 50.7%	**Risk factor/exposure 1:** n-3 fatty acids; mean values compared and OR for 1 SD difference. **Method of assessing**	**1) Follow-up rate:** 2251 with all data available out of 7814 enrolled overall **2) Important baseline differences:** Reported differences between decliners and non-decliners at	**Comments:** There are many comparisons done in this paper with only a few significant results and p-value set at 0.05. Question: Q2

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Study design: Prospective cohort **Number of participants enrolled:** 7814 2251 with all data used in this analyses **Duration of follow up:** 9 yrs overall 6 yrs for two cognitive assessments used **Time from risk factor assessment to final cognitive assessment:** 9 yrs from blood draw to final cognitive assessment used in analyses cognitive decline was measured over 6 yrs	Male: 49.3% **Race/ethnicity:** [n (%)] White 100% **Baseline cognitive status:** Those with impairment are not intentionally excluded – but given the age range of the sample at baseline, suspect most met criteria for normal cognition **Inclusion criteria**: a) complete plasma fatty acid data, b) survived to visit 4, c) complete cognitive data visits 2 and 4, e) age 50 or older at baseline **Exclusion criteria:** opposite of the inclusion criteria	**risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Smoking, ETOH, caffeine use Physical activity index BMI Dietary factors Baseline cognitive status (essentially did this but in somewhat more elaborate manner) Considered as effect modifiers: APOE Comorbid med cond **Method(s) of assessing cognitive status:** Other – Cognitive decline using Reliable change index for 3 tests: COWA, DSST, and delayed word recall test **Informant interview?:** No	baseline: Non-decliners were younger, more physically active, less depressive sxs, relatively hypocoagulable profile. Decliners had higher baseline cognitive score **3) Outcome of interest #1-** Numerous results given for comparisons (selected ones given here) a) Total PUFA- no decliners higher mean values than decliners (OR=0.55; 0.37-0.81) b)palmitic acid-no decliners lower than decliners (OR=1.28; 1.07,1.54) c) greater DHA (OR=.0.74; 0.57-0.97) and EPA (OR=0.73; 0.58-0.93) associated with less decline on verbal fluency	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Partial

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Beydoun, Kaufman, Sloane, et al., 2008 Atherosclerosis Risk in Communities (ARIC)	**Geographical location:** Four US communities (NC, MS, MN, & MD) **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 7814 **Duration of follow up:** 9 yrs **Time from risk factor assessment to final cognitive assessment:** 9 yrs but need to look at how replicate FFQ info used – cognitive decline was measured over 6 yrs	**Age:** Mean (SD): 56.6 (4.31) Median: Range: 50-65 **Sex:** [n (%)] Female: 54.6% Male: 45.4% **Race/ethnicity:** [n (%)] White 81.5% **Baseline cognitive status:** Those with impairment are not intentionally excluded – but given the age range of the sample at baseline, suspect most met criteria for normal cognition **Inclusion criteria:** a) complete dietary intake data at visit 1, b) survived to visit 4, c) complete cognitive data visits 2 and 4, e) age 50 or older at baseline **Exclusion criteria:** opposite of the inclusion criteria	**Risk factor/exposure 1:** Dietary Assessment **Method of assessing risk factor/exposure 1:** Self-report Food Frequency questionnaire **Risk factor/exposure 2:** Blood assay of dietary data **Method of assessing risk factor/exposure 2:** Self-report Direct measurement of blood pressure for all subjects and blood samples for subset at visit 1(n=2251) **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status (essentially did this but in somewhat more elaborate manner)	**1) Follow-up rate:** for self-report dietary data – 7814. For blood assay of dietary data – 2251. Only those who had all data were included in analyses. **2) Important baseline differences:** N/A **3) Outcome of interest #1-** a) adjusted analyses b) decline in word list recall modestly reduced with increase in long-chain n-3 fatty acid intake (3H) as % of total energy intake c) decline in verbal fluency reduced by increase in long-chain and all n-3 fatty acids (3H and 3) as % of total energy intake, by ratio 3H/6H and by 3Hin g day^{-1} **4) Outcome of interest #2** interaction with HTN a) finding 3b above maintained in HTN subgroup b) for DSST, interaction for ratio 3H/6H with HTN - showed less decline for HTN compared to non-HTN c) finding 3c above stronger in HTN with a sig interaction for 3H in gday $^{-1}$ **5) Outcome of interest #3** Subgroup with plasma – a) generally less decline with higher concentration of n-3 fatty acid in their plasma cholesteryl esters and	**Comments:** No results given for calibrated food frequency measures **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial for food frequency, Yes for blood assays 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes – just included those with complete data – selective attrition may have some influence 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			APOE Behavioral factors Nutritional factors Hypertension **Method(s) of assessing cognitive status:** Other – Cognitive decline using Reliable change index for 3 tests: COWA, DSST, and delayed word recall test **Informant interview?:** No	phospholipids and elevated ratio of n-3/n-6 fatty acids– but generally not significant except for verbal fluency b) for verbal fluency, HTN group showed less decline for 3H and 3H/6H for plasma cholesteryl esters and 3H/6H for plasma phospholipids	
Bierman, Comijs, Rijmen, et al., 2008 LASA Study	**Geographical location:** The Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2351 **Duration of follow up:** Up to 9 years **Time from risk factor assessment to final cognitive assessment:**	**Age:** at baseline Mean (SD): 69.5 (8.6) **Sex:** [n (%)] Female: 1097 (46.7%) Male: 1254 (53.3%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Not specified MMSE = 27.31 (2.4) **Inclusion criteria:** Random sample of 55-85 y.o. from 11 municipalities in the Netherlands	**Risk factor/exposure 1:** Anxiety at 4 time points **Method of assessing risk factor/exposure 1:** Self-report; Hospital Anxiety and Depression Scale – Anxiety subscale: 0-7=normal; 8-10 =mild anxiety, >10 = moderate/severe anxiety **Covariates/potential confounders adjusted for in analyses:** Age	**1) Follow-up rate:** 1469/2351 (62.5%) at year 9 Drop-out was associated with age, gender, education, more anxiety symptoms and lower cognitive performance **2) Important baseline differences:** NR **3) Outcome of interest #1** No significant association between anxiety symptoms and cognitive decline for any of the cognitive tests (parameter estimates not reported)	**Comments:** Subsample of LASA study; 62.3% of those invited responded; older adults and females in more urban areas were less likely to respond Analysis not limited to those with normal cognition at baseline Used random regression models **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Up to 9 years	Analyses restricted to those age 62 and older with snxiety and cognition measured at baseline **Exclusion criteria:** NR	Sex Educational level Chronic disease count Depressive symptoms Alcohol consumption Benzodiazapine use Method(s) of assessing cognitive status: Other – measured at 4 timepoints: General cognitive functioning: MMSE (0-30) Fluid intelligence: Ravens coloured progressive matrices (0-24) Processing speed: adjusted version of coding task (2-53) Episodic memory auditory verbal learning test: 3 learning trials (0-45); delayed recall (0-15) **Informant interview?:** No		cohort?: Yes 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Blair, Folsom, Knopman, et al., 2005 ARIC	**Geographical location:** Medicare files Forsyth County,NC; Jackson, MS; suburban Minneapolis, MN; Washington County, MD **Setting:**	**Age:** Mean (SD): 55 SD varied by APOE genotype **Sex:** [n (%)] Female: not specifically stated, but APOE genotype, but approximately 60%	**Risk factor/exposure 1:** APOE ε4 **Method of assessing risk factor/exposure 1:** Direct measurement Genotyping	**1) Follow-up rate:** 7895/15,792= 50% **2) Important baseline differences:** Higher cholesterol, LDL and lower HDL in E4 groups; in AAs E4 carriers had increased carotid intima-media thickness; Caucasians homozygous for E4 more likely to have diabetes and less likely to be hypertensive.	**Comments:** High dropout rate. Baseline cognitive status was not defined. Excluded people on many medications potentially biasing study. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Probability sample Community **Study design:** Prospective cohort **Number of participants enrolled:** 1693 African-Americans and 6202 Caucasians used in analysis **Duration of follow up:** 6 years **Time from risk factor assessment to final cognitive assessment:** 6 years	female in AA population; 49% women in Caucasians Male: AA ~40% White ~51% **Race/ethnicity:** [n (%)] 78.6 % white 21.4 % black **Baseline cognitive status:** Non-demented **Inclusion criteria:** Men and women age 45 to 64 at enrollment. AAs sampled exclusively in Jackson and over-sampled in Forsyth County. **Exclusion criteria:** Missing cognitive data; did not have apoe genotyping, incident or prevalent stroke, taking antidepressants, anxiolytics, sedatives, anticonvulsants, narcotics, antipsychotics, or chemotherapy.	**Covariates/potential confounders adjusted for in analyses:** Age, sex, education, baseline cognitive scores, cigarette smoking, use of NSAIDs, diabetes, hypertension, hypercholesteremia **Method(s) of assessing cognitive status:** Delayed word recall (DWR); Digit Symbol Substitution (DSS); Word Fluency (aka controlled oral word association test) **Informant Interview** No	DSS was only cognitive test different among APOE genotypes- lowest in E4/4 caucasians even after adjustment for age, sex and education. Not significant in AAs after adjustment. **3) Outcome of interest #1** AA: (adjusted for age, sex, education, education, baseline score, hypertension, DM) only the DSS showed a dose-response relation between APOE genotype and performance. E4/4 declined by 3.99 symbols, E3/3 declined by 0.98; and E2 group (E2/2 and E2/3) declined by 0.43 symbols (p=0.002) **Risk for decline in AA E4/4 compared to E3/3** DWR OR = 1.72 (95% CI 0.97-3.06) DSS OR= 1.86 (1.06-3.27) Caucasians: (adjusted for age, sex, education, education, baseline score, hypertension, DM) the DWR and DSS showed a dose-response relation between APOE genotype and performance. DSS test: E4/4 declined by 4.54; E4/2 or E4/3 group declined by 3.20 symbols, E3/3 declined by 2.69; and E2 group (E2/2 and E2/3) declined by 2.51 symbols. (p<.0001) DWR scores: E4/4 declined by .31; words; E4/2 or E4/3 group declined by .21 words, E3/3 declined by .13 words; and E2 group (E2/2 and E2/3) declined by .06 words. (p=.02)	2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				Risk for decline in Cauc. Compared to E3/3 genotype E2 group DWR OR = .78 (95% CI .61-.98); E4 group (E3/4 or E2/4) DWR OR 1.19 (1.01-1.41) and E4/4 OR DWR 1.53 (0.95-2.45) DSS OR E4/4 compared to E3/3 = 2.02 (1.31-3.12) Word fluency was not related to APOE genotype in AA or caucasians. **4) Outcome of interest #2** Interaction between APOE genotype and other risk factors. Interaction between APOE and hypercholesterolemia (p value for interaction = 0.008) Interaction between APOE genotype and diabetes mellitus (p value for interaction = 0.04)	
Blasko, Jellinger, Kemmler, et al., 2008 VITA	**Geographical location:** Vienna, Austria **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 606 **Duration of follow up:** 30 months	**Age:** Mean (SD): 75.8 (0.5) **Sex:** [n (%)] Female: 359 (59.4%) Male: 247 (40.6%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age ≥ 75	**Risk factor/exposure 1:** homocysteine ; analyzed as log transformed values **Method of assessing risk factor/exposure 1:** Direct measurement plasma stored frozen doesn't say for how long, doesn't say if fasting or not. **Covariates/potential**	**1) Follow-up rate:** 83.2% of the 119 lost to follow up, 38 died, 1 was dxd schizophrenic, 10 had only telephone interviews and 70 refused. **2) Important baseline differences:** Not clearly stated. . No information on the low vs high homocysteine at baseline groups. **3) Outcome of interest #1:** The change in homocysteine over 2.5 years for those who converted to AD: OR for AD in those with doubling of homocysteine 4.2 (1.6-11.0)	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial. Don't see information on baseline differences.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Time from risk factor assessment to final cognitive assessment: Change in homocysteine, so 0-30 months	Complete baseline data **Exclusion criteria:** Dementia Schizophrenia	**confounders adjusted for in analyses:** Age, Sex, Educational level, at least one apoE4 **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM MCI diagnosed if one of CERAD neuropsychatric test ≥ 1.5 SD below the mean **Informant interview?:** No	**4) Outcome of interest #2:** For persons who deteriorated to mci OR AD, OR for AD in those with doubling of homocysteine 2.2 (1.2-4.1), for just conversion to mci alone, table notes "no association" but data not given.	5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Can't Tell 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Borenstein, Wu, Mortimer, et al., 2005 *Kame* project (whose participants were followed in the *Ni-Hon-Sea* Project)	**Geographical location**: King County, WA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** Initial cohort of 3045 eligible participants; 1985 baseline screened; 1859 enrolled.	**Cases (n=90)** **Age:** Mean (SD): 78 yrs **Sex:** Female: 61 (68%) Male: 29 (32%) **Non Cases (n=1769)** **Age:** Mean (SD): 72 yrs **Sex:** Female: 978 (55%) Male: 791 (45%) **Race/ethnicity:** Predominantly	**Risk factor/exposure 1:** Diabetes mellitus **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2:** Is the presence of Apolipoprotein E-(ApoE) a risk factor for AD? **Method of assessing risk factor/exposure 2**	**1) Follow-up rate:** Obtained ApoE genotyping on 1111/1859(59%) **2) Important baseline differences:** NA **3) Outcome of interest #1** Cox proportional hazard models for vascular risk factors, by positive ApoE status demonstrated a HR 0.51 with a 95% CI 0.12-2.26. **4) Outcome of interest #2** The risk for AD was stronger for women who carried ApoE 4 allele than for men.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?:

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Duration of follow up: Cognition was assessed at baseline and at each of four follow up waves. Subjects with a score of >87/100 were followed every 2 yrs. Those with scores of 87 or less at any biennial follow up were then evaluated with a full evaluation. Total follow up: 6 yrs **Time from risk factor assessment to final cognitive assessment:** 6 yrs(SD =2.7)	Japanese American **Baseline cognitive status:** Non-demented **Inclusion criteria:** 65 yrs and older; free of AD at baseline **Exclusion criteria:** NR	Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status Developmental risk factors Vascular risk factors **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM-IV Other – Cognitive Abilities Screening Instrument(CASI) **Informant interview?:** No	Women who carried an ApoE 4 allele was also higher (HR=2.37,95%CI 0.93-6.01,p=0.07) than for those who did not (HR=0.98,95%CI 0.47-2.04) Women who were negative for ApoE 4 allele: HR 0.98, 95%CI 0.47-2.04, p=0.95.	Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial; genotyping obtained on 59% 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Bosma, van Boxtel, Ponds, et al., 2002 Maastricht Aging Study" (MAAS)	**Geographical location:** The South of the Netherlands **Setting:** Clinical –Family practice clinics. **Study design:** Prospective cohort	**Age:** Range: > 50 (49 – 81 at baseline) Since they stratified the sample, it is hard to get a specific age number. **Sex:** Both genders included; no specific numbers reported	**Risk factor/exposure 1:** Physically active sports **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2:** mentally active sports	**1) Follow-up rate:** 1069 participants recruited. 138 refused. 50 died during follow up period and 8 developed dementia. Therefore, only 830 (77.64%) persons were used in the analysis. **2) Important baseline differences:** NR **3) Outcome of interest #1:** Physical activities were significantly	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial, selection methods missing some detail 2) Selection minimizes baseline differences in prognostic factors?: Yes. 3) Sample size calculated/5%

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Number of participants enrolled: 1823 enrolled of whom, 1069 met inclusion criteria. **Duration of follow up:** 3 years. **Time from risk factor assessment to final cognitive assessment:** 3 years	**Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** >50 yrs **Exclusion criteria:** Chronic neurological pathology Mental retardation Chronic psychotropic drug use Dementia	(e.g., chess, puzzles) **Method of assessing risk factor/exposure 2:** Self-report **Risk factor #3:** organizational memberships (e.g., clubs) **Method of assessing risk factor/exposure 3:** Self report. **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status Length of follow up interval. **Method(s) of assessing cognitive status:** Other – Stroop Color – Word Test (interference sub-task) , the Verbal Learning Test (immediate and delayed recall sub-tasks) , the Letter Digit	associated with the letter digit coding. β = 0.82 p <0.05 **4) Outcome of interest #2** Mental activities were significantly associated with Letter digit coding β = 0.1.18 p <0.01 and MMSE β = 0.40 p <0.01. **5) Outcome of interest #3** Social activities were significantly associated with total recall β = 0.94 p <0.05 and Delayed recall β = 0.30, p <0.05 **6) Outcome of interest #4** Number of activities treated as a continuous variable was associated with Letter digit coding β = 0.66, p <0.01, Word fluency β = 0.34, p <0.05, Delayed recall β = 0.16, p <0.05 and MMSE β = 0.17, p <0.01	difference?: No 4) Adequate description of the cohort?: No 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Coding Test , the Word Fluency Test ,and the Mini-Mental State Examination **Method of assessing dementia:** NR **Informant interview?** No		
Breitner, Haneuse, Walker, et al., 2009 Adult Changes in Thought (ACT)	**Geographical location:** Seattle, WA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3392 (1994-2003) 2581 from 1994-6 811 from 2001-3 **Duration of follow up:** Up to 12 years Original cohort=10-12 Expansion cohort=3-5 **Time from risk factor assessment to final cognitive assessment:** between 3 and 12 years	**Age:** Median: 74.8 Range: ≥ 65 y **Sex:** [n (%)] Female: 1636 (59.8) Male: 1100 (40.2) **Race/ethnicity:** [n (%)] White : 2473 (90.4) Other: 263 (9.6) **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 yo Membership in group health plan of ≥10 y At least one follow-up visit **Exclusion criteria:** Presence of dementia or AD	**Risk factor/exposure 1:** NSAIDs prescribed and/or used over time **Method of assessing risk factor/exposure 1:** NSAID use Self-report Medical record classified as heavy use (≥ 500 Standard daily doses within 2 years); moderate 60-499 SDD; light <60 SDD **Covariates/potential confounders adjusted for in analyses:** (Analysis was stratified by age) Race Sex Educational level Comorbidities plausibly	**1) Follow-up rate:** For primary analysis: At least one F/U visit= 90% By end of study, 10% withdrew and 24% had died For secondary analysis: Two or more F/U visits = 69% **2) Important baseline differences:** None with standard demographics Degree of NSAID exposure - decreased with (no surprises) Exercise, smoking, normal wt - increased with (no surprises) Limitation in AODL, obesity, total prescriptions, use of H2 blockers or proton pump inhibitors, Dx of osteoarthritis At baseline, 50% were non or light users of NSAIDs, 37% were moderate users, and 13% were heavy users **3) Outcome of interest #1** All-cause Dementia using pharmacy	**Comments:** Results did not differ significantly when pharmacy + self report data used Cohort with health insurance **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: No explanation given why there was an expansion cohort, but was adjusted for in analysis 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			assoc'd with NSAIDs or dementia APOE status **Method(s) of assessing cognitive status:** 2-stage evaluation with CASI, then diagnostic evaluation for CASI ≤ 85; NINCDS-ADRDA DSM-IV **Informant interview?:** No	data 476 (17%) In all 3 models, no reduction in risk of dementia among NSAID users; in fact, risk appears to increase c use M1 – low=1.00; mod= 1.13 (0.92-1.38); heavy=1.51 (1.18-1.94) M2– low=1.00; mod= 1.09 (0.88-1.35); heavy=1.48 (1.13-1.93) M3– low=1.00; mod= 1.13 (0.90-1.43); heavy=1.66 (1.24-2.24) This result was robust in 2° analyses **4) Outcome of interest #2** Alzheimer's Disease 356 of 476 (13%) attributed to AD Dementia using pharmacy data In all 3 models, no reduction in risk of dementia among NSAID users; in fact, risk appears to increase c use M1 – low=1.00; mod= 1.17 (0.92-1.47); heavy=1.40 (1.05-1.87) M2– low=1.00; mod= 1.18 (0.92-1.52); heavy=1.38 (1.01-1.89) M3– low=1.00; mod= 1.26 (0.97-1.65); heavy=1.57 (1.10-2.23) This result was robust in 2° analyses	8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes, Cox proportional hazards models stratified by age with time-dependent covariates. Did not include NSAID use in last year prior to Dx to avoid confounding from suspected interaction between NSAID and AD. Secondary analyses were done to explore interactions with age, test influence of H2 blockers and proton pump inhibitors, recency of exposure, specific NSAID mode of action, time-frame of enrollment and criteria used to dx AD
Bretsky, Guralnik, Launer, et al., 2003 MacArthur Successful Aging Study	**Geographical location:** Durham, NC, East Boston, MA, New Haven, CT **Setting:** Community **Study design:** Prospective cohort	**Age:** Mean (SD): E4+ 73.8 (2.7) E4- 74.1 (3.0) Range: 73-79 **Sex:** [n (%)] Female: 539 (44%) Male: 426 (56%) **Race/ethnicity:** [n (%)]	**Risk factor/exposure 1:** Apolipoprotein E genotype **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential**	**1) Follow-up rate:** 88.8% at 3 years and 67.1% at 7 years **2) Important baseline differences:** Distribution of E4 carriers was different by ethnicity **3) Outcome of interest #1** Adjusted OR (95% CI) at year 3 in APOE e4 vs non-e4:	**Comments:** Participants were selected to be in top 1/3 of population, so applicability to general population is limited. Baseline cognitive status assessed by 9 question SPMSQ. To participate, subjects had to have score ≥6, which may not exclude mild dementia.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Number of participants enrolled: 965 **Duration of follow up:** 7 years **Time from risk factor assessment to final cognitive assessment:** Not stated when genotyping was performed	725 (75%) white 234 (24.4%) black 6 (0.6%) other **Baseline cognitive status:** Participants who scored in the top third of the cognitive and physical screening tests for their age group **Inclusion criteria:** Age 70-79 in 3 communities. Aim is to identify those in the top 1/3 of population. No reported disability on 7 item ADL; no more than 1 reported mild disability on 8 items of tapping, gross mobility and ROM; ability to hold a semi-tandem balance for at least 10 seconds; ability to stand from a seated position five times in 20 seconds. Cognitive criteria include scoring 6 or more on SPMSQ; remembering 3 or more of 6 elements on a delayed recall of a short story **Exclusion criteria:** NR	**confounders adjusted for in analyses:** Age Race Sex Educational level **Method(s) of assessing cognitive status:** Other – Short Portable Mental Status Questionnaire (SPMSQ); Abstraction (based on four items from similarities test of Wechsler adult intelligence scale-revised (0-16 points); delayed spatial recognition (0-17); language (Boston naming test; 0-18); spatial ability (0-20). Two summary scores were made from the subscores. Total cognition included sum of all subscores (0-89). Total memory score is composed of sum of delayed incidental and spatial recall (0-31). Decline on SPMSQ was defined as a score ≤6. A decline in other domain was defined as ≥1 SD decline from baseline score.	Only Naming (OR=2.7; CI = 1.2 -5.9) and Copying figures (OR =1.8; CI = 1.1-3.1) showed significant differences. Adjusted OR (95% CI) Odds of cognitive decline at year 7 In APOE e4 vs non-e4 SPMSQ 2.3 (1.5-3.4) Total cognition 2.0 (1.1-3.6) Memory 1.7 (1.1-2.5) Naming 2.5 (1.5-4.2) Figures 2.1 (1.4-3.3) Similarity 1.8 (1.1-3.1) Not significant difference Story recall 1.4 (0.9-2.1) Spatial recognition 1.3 (.9-2.0)	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yyes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Informant interview?: No		

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Carmelli, Swan, Reed, et al., 1998 National Heart Lung and Blood Institute Twin Study (WW II veterans sub-study)	**Geographical location:** USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 410 **Duration of follow up:** 10 years **Time from risk factor assessment to final cognitive assessment:** 10-25 years	**Age:** Mean 63.2 (2.9) Range: 73 and up **Sex:** [n (%)] Female: 0 (0%) Male: 410 (100%) **Race/ethnicity:** [n (%)] White: 410 (100%) **Baseline cognitive status:** did not eliminate cognitive impaired but mean age was 63.1 (2.9) and mean mmse 27 for overall group. **Inclusion criteria:** Participating in National Heart, Lung, and Blood Institute Twin Study Evaluated for cognitive function at third and fourth cardiovascular exam **Exclusion criteria:** See NHLBI Twin Study, Reference 16	**Risk factor/exposure 1:** htn **Method of assessing risk factor/exposure 1:** mean bp >140/90 or use of antihypertensive medication at any of the exams on or prior to baseline cognitive assessment (10-25 years before f/u cognitive assessment) **Risk factor/exposure 2:** dm **Method of assessing risk factor/exposure 2:** 1 hour post prandial glc > 200 or use of hypoglycemic agent or insulin. **Covariates/potential confounders adjusted for in analyses:** Age,Race,Sex, baseline score, incident CVD **Method(s) of assessing cognitive status:**	**1) Follow-up rate:** 410/589, 69.6% **2) Important baseline differences:** baseline difference are given for apoE4 present and absent and the only significant difference was more errors in Benton visual retention test for those without apoE4 **3) Outcome of interest #1** hyperglycemics experienced a significantly greater decline on dss, bvrt and mmse. **4) Outcome of interest #2** hypertensives also experienced a greater decline on the dss but not mmse and bvrt. p values (non-exact) are given for one sided significance **5) Outcome of interest #3** Subjects with dm and htn had a greater decline on the dss than those with neither risk factor and more than expected for both combined (but not significant) Mean change (SD) APOEe4 + and Hyperglyc present MMSE 1.66 (.39) DSS 7.84 (1.08) BVRT 1.05 (.26) APOEe4+ and hyperglyc absent MMSE 0.73 (.28) DSS 4.47 (.76) BVRT .53 (.19)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial, WWII veteran male twins 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Ppartial 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			change in test scores **Informant interview?:** No	APOEe4 – and hyperglyc present MMSE .47 (.2) DSS 4.14 (.56) BVRT .84 (.14) APOEe4- and hyperglyc absent MMSE .47 (.16) DSS 3.34 (.45) BVRT .37 (.11) All scores are significantly different from 0 and statistically significant at p<.05	
Cherbuin, Reglade-Meslin, Kumar, et al., 2009	**Geographical location:** Canberra and Queanbeyan, Australia **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2082 (analytical sample) **Duration of follow up:** 4 yrs **Time from risk factor assessment to final cognitive assessment:** 4 yrs	**Age:** Mean (SD): Normal Wv 2: 62.5(1.5) Mild-impaired Wv2: 62.53(1.6) **Sex:** Female: 1020 (48.99%) Male: 1062 (51.01%) **Race/ethnicity:** [n (%)] White: 1910 (91.7%) Other: 172 (8.3%) **Baseline cognitive status:** Cognitively normal **Inclusion criteria:** At baseline, age 60-64 and cognitively normal **Exclusion criteria:** None except as covered by inclusion criteria	**Risk factor/exposure** Alcohol Smoking Anxiety medication Anxiety and depressive symptoms **Method of assessing risk factor/exposure 1** Self-report for alcohol using the AUDIT interview Self report for smoking Unclear how medication use was obtained Anxiety and depressive symptoms – Goldberg anxiety/depression scales-threshold for significant symptoms not reported Blood pressure measured **Covariates/potential confounders adjusted for in**	**1) Follow-up rate:** 2082/2551 (81.7%) **2) Important baseline differences:** Reported differences by outcome not by exposure **3) Outcome of interest #1** Incident MCI (18 incident cases): alcohol intake associated with lower risk of MCI (OR=0.59; 95% CI 0.37-0.92; p=0.021) Quadratic model – U-shaped association showing higher risk for low and high drinking groups (OR=1.58; 1.18-2.11; p=0.002) Past smoking (OR3.22; 1.05-9.87) Anxiety medication (OR 3.58; 0.97-13.22) Goldberg depression scale (OR 1.54; 1.07-2.22) and anxiety scale (OR 0.83; 0.58-1.18), antidepressant medication (OR 2.79; 0.38-20.57), Diabetes (OR 0.53; 0.06-4.6), BMI (OR 1.01; 0.91-1.11) reported in full but not reduced model used for other results.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial, only some measures validated 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?:

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			analyses: Age Sex Educational level **Method(s) of assessing cognitive status:** DSM Other – published criteria for MCI, AAMI, AACD and other cognitive disorder **Informant interview?:** Yes (when available)	**4) Outcome of interest #2** Incident any mild cognitive disorder(MCD, n=64): alcohol intake associated with lower risk (OR=0.75; 0.57-1.00; p=0.046) Diastolic Blood pressure (OR 0.96; 0.92-0.99) Past smoking (OR 1.97; 1.12-3.44) Antidepressant medication (OR 3.25; 1.51-7.00) Anxiety medication (OR 0.67; 0.2-2.28), Goldberg depression scale (OR 1.16; 0.96-1.4) and anxiety scale (OR 0.93;0.79-1.1), diabetes (OR 1.09; 0.48-2.44), BMI (OR 1.03; 0.98-1.07) reported in full but not reduced model used for other results. Quadratic model – U-shaped association showing higher risk for low and high drinking groups (OR=1.17; 0.98-1.40; p = 0.087)	Partial, for MCI too many candidate independent variables for the number of incident cases
Christensen, Batterham, Mackinnon, et al., 2008	**Geographical location:** Canberra and Queanbeyan Australia **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2551	**Age:** Mean (SD): 60-64 **Sex:** [n (%)] Female: 1329 (51.72%) Male: 1232 (48.28%) (This is based on the first wave). **Race/ethnicity:** [n (%)] All Caucasian **Baseline cognitive status:**	**Risk factor/exposure 1:** Genotype **Method of assessing risk factor/exposure 1:** Direct measurement Cheek swab **Risk factor/exposure 2:** Education Head Injury Premorbid intelligence	**1)Follow-up rate:** 2551 in the first wave and 2222 in the second wave. Of the 770 234 refused or were unable to be interviewed due to medical reasons, 25 could not be located and 70 died . The rest were excluded due to study design reasons. **2) Important baseline differences:** None **3) Outcome of interest #1** After controlling for Head Injury, education and premorbid	**Comments:** There is no correction for multiple comparisons in this study therefore, they may be spurious findings. Head injury was assessed based on one self report question. This may not be an adequate measure of exposure. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Duration of follow up: 4 years **Time from risk factor assessment to final cognitive assessment:** 4 years	All **Inclusion criteria:** 60-64% Alive at the time of second survey Those who were not genotyped **Exclusion criteria:** NR	**Method of assessing risk factor/exposure 2:** Self-report Direct Measurement **Covariates/potential confounders adjusted for in analyses:** Educational level Head Injury Premorbid intelligence **Method(s) of assessing cognitive status:** Other – change on word list memory task, MMSE, SDMT, Digit Span Backwards, Reaction time task **Informant interview?:** Yes	intelligence, the APOE genotype was associated with change in Symbol Digit Modalities Test (SDMT) F=3.20 and p= 0.041 and digit span backwards F= 3.14, p = 0.44. **4) Outcome of interest #2** After controlling for cofactors, education was not associated with change scores in any of the cognitive tests. **5) Outcome of interest #3** After controlling for cofactors, head injury was associated with change score in MMSE F = 4.91, p = 0.027	differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: no 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial 10) Analysis controls for confounding?: No 11) Analytic methods appropriate?: No
Christensen, Henderson, Korten, et al., 1997	**Geographical location:** Canberra and Queanbeyan, Australia **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:**	**Age:** Range: 70 – 97 years **Sex:** [n (%)] Female: NR Male: NR **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non demented	**Risk factor/exposure 1:** Depression 2: Anxiety **Method of assessing risk factor/exposure** 18- item interview Goldberg Depression & Anxiety questionnaire; threshold for positive not specified **Covariates/potential**	**1) Follow-up rate:** 612/897=68% of total and 83% of those alive (124 died; 129 lost to f/u; 32 only informant data) **2) Important baseline differences:** NR **3) Outcome of interest #1** Mild Cognitive Impairment (26 cases); multiple logistic regression analysis evaluating: age, education, anxiety, depression, only age was	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: No 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	897 **Duration of follow up:** Mean 3.6 years, range 3.3 to 4.2 years **Time from risk factor assessment to final cognitive assessment:** Mean 3.6 years	MCI **Inclusion criteria:** "sample of 897 elderly persons" **Exclusion criteria:** NR	**confounders adjusted for in analyses:** Age Educational level Method(s) of assessing cognitive status: Mild cognitive impairment based on 4 criteria: 1. Report of neurological or other physical diseases causing cerebral dysfunction 2. Decline in cognition reported by subject or informant 3. >1.5 below mean on 2 of 12 cognitive tests 4. Met ICD-10 criteria for dementia or probable dementia, DSMIIR delirium or amnestic syndrome. **Informant interview?:** Yes, for some subjects	significantly associated with incident MCI- OR 1.09 per year (CI 1.01 to 1.18). Parameter estimates not given for other risk factors.	cohort: No 5) Validated method for ascertaining exposure: Yes 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Yes 9) Completeness of follow-up: No 10) Analysis controls for confounding: Partial 11) Analytic methods appropriate: Partial
Clarke, Birks, Nexo, et al., 2007	**Geographical location:** Oxford, United Kingdom	**Age:** Mean (SD): 71.9 (5.2) for analytical sample **Sex:** [n (%)]	**Risk factor/exposure 1:** B-12, folate, homocysteine, holotranscobalamin,	**1) Follow-up rate:** 691/1344 (51%), but not all of those gave blood **2) Important baseline differences:**	**Comments:** Question 2 **Quality assessment:** *For observational studies:*

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Oxford Healthy Aging Project	**Setting:** Clinical – from general medical practice registry **Study design:** Prospective cohort **Number of participants enrolled:** 691 – analytical sample **Duration of follow up:** 10 years **Time from risk factor assessment to final cognitive assessment:** 8 years	Female: 60.4 Male: 39.6 **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age aged 65 or older at baseline. Randomly selected from general practice registers for people living in Oxford city. Completed blood draw at Year 2 and completed MMSE year 1 and year 10. **Exclusion criteria:** Participants (*n* = 9) with extreme elevations of vitamin B-12 (>1000 pmol/L) or holoTC (>400 pmol/L) or who reported use of vitamin B-12 injections or any B-vitamin supplements (*n*=22)	methylmalonic acid **Method of assessing risk factor/exposure 1:** Direct measurement, non-fasting at year 2 **Covariates/potential confounders adjusted for in analyses:** Age Sex Smoking Vascular disease, Systolic blood pressure Education APOE Levels of other vitamins being assessed **Method(s) of assessing cognitive status:** Other – change in MMSE **Informant interview?:** No	NR **3) Outcome of interest #1** Doubling in thcy was associated with a > 50% more rapid cognitive decline **4) Outcome of interest #2** Cognitive decline was not associated with serum concentrations of thcy after adj for other markers of vitamin status	1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Comijs, Kriegsman, Dik, et al., 2009 LASA	**Geographical location:** 11 municipalities throughout the Netherlands **Setting:**	**Age:** Mean (SD): 72.1 (6.5) Range: 62-85 **Sex:** [n (%)] Female: 668 (51.6%) Male: 626 (48.4%)	**Risk factor/exposure 1:** presence of chronic disease – a) cardiac disease, b) peripheral artheroschlerosis,	**1) Follow-up rate**: At T1 = 95.3% At T2 = 95.4% At T3 = 74.8% Follow-up rate for those eligible at baseline is uncertain	**Comments:** Subjects who were excluded for insufficient data at after baseline were older, had less education, had limited vision, were more often women, and had lower test scores at baseline.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Community **Study design:** Prospective cohort **Number of participants enrolled:** 2429 at baseline 1358 with complete data at 2 time-points were analyzed: T1 = 1294 data points T2 = 1296 data points T3 = 1016 data points **Duration of follow up:** 1993-1999 T1 = 1992/93 T2 = 1995/96 T3 = 1998/99 **Time from risk factor assessment to final cognitive assessment:** 6 yr	**Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** NR (Referring to Knipscheer, 1995 – original article given at a congress and published in Dutch) **Inclusion criteria:** Member of cohort recruited for NESTOR-LSN study (Knipscheer, 1995) Age 50-85 **Exclusion criteria:** Born after 1930 Only one measurement time-point	c)stroke, d) DM, e) COPD, f) arthritis, g) cancer. **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age, Sex Educational level Presence of comorbid disease outside of the 7 of interest Smoking Alcohol use Antidepressant meds Benzodiazepines Depressive sx (CES-D) Impaired vision Impaired hearing Mobility (6 AODL) **Method(s) of assessing cognitive status:** Other – Outcome 1: General Cognition -Mini-Mental State Exam (Folstein, 1975) O. 2: Fluid intelligence -Raven's Colored Progressive Matrices (Raven, 1995) O.3: Processing speed	**2) Important baseline differences:** NR **3) Outcome of interest #1** General cognitive function over time: Negatively affected by DM (-0.49, CI -0.86/-0.11) **4) Outcome of interest #2** Fluid intelligence over time: Negatively affected by DM (-1.03, CI -1.54/-0.51) & stroke (-073, CI -1.32/-0.14) **5) Outcome of interest #3** Information processing speed over time: negatively affected by PVD (-0.73, CI -1.43/-0.03), stroke (-1.97 CI -2.78/-1.16) and DM (-0.76, CI -1.53/0.00) **6) Outcome of interest #4** Memory performance (immediate and delayed recall) over time: Immediate- Negatively affected by DM (-0.44, CI -0.83/-0.06); positive association with cardiac disease (0.32, CI 0.11/0.52) Delayed – Negatively affected by DM (-0.65, CI -0.95/-0.17); positive association with cardiac disease (0.23, CI 0.005/0.45) and cancer (0.32, CI 0.08/0.67) Positive associations were the weakest reported; interactions showed faster rates of decline in immediate recall with PVD, information processing speed and	Also, over F/U measurements, those measured with chronic disease increased from 29.9 to 52.8%, current smokers decreased and psychotropic drug use increased Generalized Estimated Equations take into account repeated measure and missing data (Twisk, 1997); also tested each potential cofactor before adding to the model and tested interactions **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Can't Tell 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial, race not given 5) Validated method for ascertaining exposure?: Partial, self-report 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes at T2, no at T3 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			- Alphabet Coding Task (Savage, 1984) O.4: Auditory Verbal Learning Test (Rey, 1964) **Informant interview?:** NR (but the interviews took place in the subject's home)	memory with stroke, delayed recall with DM, and immediate recall with cancer.	
Commenges, Scotet, Renaud, et al., 2000 Paquid Study	**Geographical location:** Gironde & Dordogne districts of France **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3777 in overall study but 1367 meet criteria for current analyses **Duration of follow up:** 2-5 yrs **Time from risk factor assessment to final cognitive assessment:** 2 – 5 yrs	**Age:** Mean (SD): 76 yr **Sex:** [n (%)] Female: 801 (59%) Male: 566 (41%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 yr Living at home For current analyses- had to have completed nutrition questionnaire, not be demented at 3-yr fup, and have covariate info available, and were seen at one of the visits after 3-yr fup **Exclusion criteria:** Opposite of inclusion	**Risk factor/exposure 1:** flavonoids **Method of assessing risk factor/exposure 1:** Self-report (2 different questionnaires for subsets of sample) **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Weight Vitamin C **Method(s) of assessing cognitive status:** DSM **Informant interview?:** No	**1) Follow-up rate:** 1367 used in analyses. Difficult to assess follow-up rate because this is a subset of larger sample **2) Important baseline differences:** NR **3) Outcome of interest #1** Flavonoid values in the upper 2 tertile-level were associated with lower rate of dementia (RR=0.49;0.26-0.92)	**Comments:** Question 1 Flavonoid quantities estimated from food frequency questionnaires and by imputing values using a "percentile method" – validity is uncertain **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		criteria			10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Cornelius, Fastborn, Winblad, et al., 2004 Kungsholmen Project	**Geographical location:** Stockholm, Sweden **Setting:**] Community **Study design:** Prospective cohort **Number of participants enrolled:** 1301 **Duration of follow up:** Baseline 10/87 First follow up 91-93 Second f/up 94-96 **Time from risk factor assessment to final cognitive assessment:** nsaid exposure recorded baseline and first follow up. 2-9 years from time of risk factor assessment at baseline to final cognitive assessment	**Age:** Range: 74 – 85+ **Sex:** [n (%)] Female: 976 (75%) Male: 325 (25%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** All inhabitants of Kungsholman Parrish, Stockholm in Oct 1987 who were born in 1912 or before, including institutionalized residents. Unfortunately, I can't tell how many were institutionalized. **Exclusion criteria:** it NR	**Risk factor/exposure 1:** nsaid **Method of assessing risk factor/exposure 1:** Self-report Inspection of pill bottles. **Covariates/potential confounders adjusted for in analyses:** Age Sex Underlying disease Educational level **Method(s) of assessing cognitive status:** DSM **Informant interview?:** Yes	**1) Follow-up rate:** 50% at six years (approx) but only 3.5% due to drop-out; others demented or deceased so were not followed, 88% at first follow up **2) Important baseline differences:** NR **3) Outcome of interest #1** ASA AD 1.34(0.96-1.89) **4) Outcome of interest #2** NSAIDs 0.61 (0.32-1.15) **5) Outcome of interest #3** ASA or NSAIDs 1.11 (0.81-1.52) **6) Outcome of interest #4** RR of AD with asa use if E4 negative: 1.80 (1.14-2.83)	**Comments:** **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Dai, Borenstein, Wu, et al.,	**Geographical location:** King County,	**Age:** Mean (SD): 71.8	**Risk factor/exposure 1:** Dietary intake of a	**1) Follow-up rate:** Initial cohort of 3045 enumerated in a census, representing 90% of the	**Comments:** Fruit juice consumption was not an a priori hypothesis. This potential

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
2006 Kame Project	Washington **Setting:** Community **Study design:** Prospective cohort . Baseline, with 4 f/u waves 2 years apart. **Number of participants enrolled:** 1836 enrolled. Data from 1589 (86.5%) **Duration of follow up:** 6.3 yrs (SD 2.6) **Time from risk factor assessment to final cognitive assessment:** 6.3 yrs (SD 2.6)	**Sex:** Female: 864 (54.4%) Male: 726 (45.6%) **Race/ethnicity:** Japanese American **Baseline cognitive status:** Non-demented **Inclusion criteria:** Japanese Americans (self-identified in the US Census) in King County, WA, aged ≥ 65 yrs **Exclusion criteria:** Dementia at baseline.	variety of foods **Method of assessing risk factor/exposure 1:** Self-report. Food frequency questionnaire. Each food item has 8 frequency options and 3 usual portion sizes. Intake of nutrients calculated from these data. 3 categories of frequency: 1) Less than weekly (reference) 2) 1-2 times/wk 3) ≥ 3 times/wk **Risk factor/exposure 2:** APOE status **Method of assessing risk factor/exposure 2:** Direct measurement on 1047 of the 1589 (65.9%) participants with complete food diaries **Covariates/potential confounders adjusted for in analyses:** Age,	Japanese American population in King County in 1990. Of these, 1985 (65.2%) participated in the baseline study, of whom 1836 (60.3%) were dementia free and comprise the analytical sample. Of 1836 dementia-free participants, food intake data available from 1589 (86.5%) **2) Important baseline differences:** NA **3) Outcome of interest #1** 81 incident cases of probable AD, 63 of which completed the food diary and are included in the analyses. **4) Outcome of interest #2** HR for incident probable AD by frequency of intake Fruit and vegetable juice: 1) 1-2 x's/wk: HR 0.84 (95% CI: 0.31-2.29) 2) ≥3 x's/wk: HR 0.24 (0.09-0.61) Tea drinking: 1) 1-2 x's/wk: HR 1.49 (95% CI: 0.43-5.16) 2) ≥3 x's/wk: HR 1.70 (0.67-4.33) Wine (sake) drinking: 1) 1-2 x's/wk: HR 0.49 (95% CI: 0.11-2.10) **5) Outcome of interest #3** Author's conclusions: "We found that frequent drinking of	relationship with AD risk emerged after analysis of many different dietary factors. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes. Instrument validated on a separate sample. 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Dietary factors, Tobacco and alcohol, education, physical activity, APOE status **Method(s) of assessing cognitive status:** CASI to assess cognition at baseline and f/u. Further w/u if scored ≤87. Dx by Consortium to Establish a Registry for Alzheimer's Disease criteria. NINCDS-ADRDA DSM-IV **Informant interview?:** Yes, using the Clinical Dementia Rating Scale	fruit and vegetable juices was associated with a substantial decrease of AD. This inverse association was stronger after adjustments for potential confounding factors."	
de Lau, Smith, Refsum, et al., 2009	**Geographical location:** Rotterdam, The Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1019	**Age:** Mean (SD): 72.2 (7.4) Median: NR Range: 60-90 **Sex:** [n (%)] Female: 530 (52) Male: 489 (48) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented	**Risk factor/exposure 1:** Plasma B12 (and transport; metabolites transcobolamin and holotranscoboloamin, methylmalonic acid) **Method of assessing risk factor/exposure 1:** Microbial assay **Covariates/potential confounders**	**1) Follow-up rate:** 832/1019 (81.6%) **2) Important baseline differences:** B12 deficiency associated with older age and white matter lesions on MRI **3) Outcome of interest #1** Follow-up cognition No association was observed for any of the studied variables (including plasma B12 analyzed by quintiles) with rate of cognitive decline during follow-up…data not shown.	**Comments:** Question 2 – no cat Dx **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes, stated as random 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial, race not given 5) Validated method for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Duration of follow up: 7 years 1995-96 assembled 2001-2003 **Time from risk factor assessment to final cognitive assessment:** 7 yr	**Inclusion criteria:** Age, 60-90 y **Exclusion criteria:** Dementia blindness	**adjusted for in analyses:** Age, sex, education, creat holoTC, homoCys, folate, DM, BP, Alcohol use, smoking, vitamin supplements, depression, intima-media thickness **Method(s) of assessing cognitive status:** Neuropsych tests to measure global cognitive function derived by combining z scores for all tests below- (Stroop test, Letter-Digit Substitution, Verbal fluency, Memory Scanning, memory function with 15-word verbal learning task for immediate and delayed recal **Informant interview?:** No		ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell, but probably yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Partial, no adjustment for multiple comparisons
DeKosky, Williamson, Fitzpatrick, et al., 2008	**Geographical location:** 4 US academic medical centers (MD, PA, CA, & NC)	**Age:** Mean (SD): 79.1 (3.3) **Sex:** [n (%)] Female: 46% Male: 54%	**Risk factor/exposure 1:** ginkgo biloba **Method of assessing risk factor/exposure**	**1) Follow-up rate:** 379 died – not sure from which groups. States knew cognitive status of 93.6% participants at trial end. 1426/1524 placebo 1448/1545 GB	**Comments:** None **Quality assessment:** *For RCTs:* 1) Baseline comparability?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Ginkgo Evaluation of Memory Study	**Setting:** Community **Study design:** RCT **Test intervention:** Twice-daily doses of 120-mg G bilboa extract (EGb 761; Schwabe Pharmaceuticals) **Comparator intervention(s):** Identically appearing placebo **Number of participants enrolled:** 3069 **Duration of follow up:** Median 6.1 yrs **Time from risk factor assessment to final cognitive assessment:** median follow-up was 6.1 yrs (max = 7.3 yrs)	**Race/ethnicity:** [n (%)] White 2930 (95%) Nonwhite 139 (5%) **Baseline cognitive status:** Normal MCI **Inclusion criteria:** Aged 75 or older, on voter registration list or purchased mailing list; have willing proxy to be interviewed every 6 mos **Exclusion criteria:** Prevalent dementia (meeting DSM-IV criteria for dementia or a score >0.5 on the CDR; currently taking warfarin; taking cholinesterase inhibitors for cognitive problems or dementia; unwilling to discontinue taking over-the-counter G bilboa for the duration of study; currently being treated with tricyclic antidepressants, antipsychotics, or other medications with significant psychotropic or central cholinergic effects; daily use of more than 400-IU	**1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Race Sex MCI APOE Cardiovascular disease **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes	**2) Important baseline differences:** none **3) Outcome of interest #1** No difference in rate of AD by intervention for all participants No difference in rate of AD by intervention for baseline normal group No difference in rate of AD by intervention for baseline MCI group **4) Outcome of interest #2** No interaction by age, sex, or MCI for results in 3) above by	2) Valid AD/cognitive outcomes assessment?: Yes 3) Subjects/providers blind?: Yes 4) Outcome assessors blind?: Yes 5) Incomplete data adequately addressed?: Yes 6) Differential dropout rate < 10%?: Yes 7) Overall dropout rate < 30%?: Yes 8) Conflict of interest reported and insignificant?: Yes 9) Randomization adequate?: Yes 10) Allocation concealment adequate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		vitamin I or unwillingness to reduce intake to this level; history of bleeding disorders; hospitalization for depression within the last yr or electroconvulsive therapy within last 10 yrs; history of Parkinson disease or taking anti-Parkinson medications; abnormal thyroid tests, serum creatinine level greater than 2.0 mg/dL, or liver function tests more than 2 times the upper limit of normal at baseline; baseline vitamin B_{12} levels 210 pg/mL or lower; hematocrit level less than 30%; platelet count lower than 100x103/μL; disease-related life expectancy of less than 5 yrs; known allergy to G bilboa			
Devore, Grodstein, van Rooij, et al., 2009 Rotterdam Study	**Geographical location:** Ommoord (Rotterdam), Netherlands **Setting:** Community	**Age:** Mean (SD):8.2 Range: 67 – 88.3 **Sex:** [n (%)] Female: 3184, 59% Male:2211, 41%	**Risk factor/exposure 1:** Consumption of fish and omega-3 polyunsaturated fatty acids (PUFAs) **Method of assessing**	**1) Follow-up rate:** 5395/6444=83.7.5% - Of the 7963 individuals who agreed to participate, 7046 underwent cognitive screening and were free of dementia. 6444 eligible for dietary history -Final population for analysis = 5395	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Dietary consumption of fish and omega-3 PUFA's in relation to long-term risk of dementia	**Study design:** Prospective cohort **Number of participants enrolled:** 5395 **Duration of follow up:** 9.6 years **Time from risk factor assessment to final cognitive assessment:** 14 years	**Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participants in the Rotterdam study, aged≥55 years who were free of dementia and reported dietary information at baseline **Exclusion criteria:** -Questionable cognitive status (score of <80 on the Cambridge examination of mental disorders of the elderly, Camdex) -living in a nursing home -lack of reliable dietary information	**risk factor/exposure 1:** Self-report 2-step protocol consisting of home interview and a validated semi-iquantitative food-frequency questionnaire administered by a trained dietician at the time of clinical examination. **Covariates/potential confounders adjusted for in analyses:** -Age -Sex -Education -Total energy intake -Alcohol intake -Smoking -Body mass Index (BMI) -High total cholesterol -Hypertension -Dietary intake of Vitamin E -Supplement use (either fish, omega-3, or antioxidant supplements) -History of stroke, myocardial infraction, or type 2 diabetes **Method(s) of assessing cognitive**	**2) Important baseline differences:** -Participants with greater fish intake also tended to consume more alcohol **3) Outcome of interest #1** - Dementia developed in 465 participants (365 with diagnosis of AD) -Total fish and omega-3 PUFA intake unrelated to AD risk. HR for high (>sex-specific median) intake 0.99 (0.76-1.29), low intake HR 1.05 (0.83-1.37) compared to no intake No association between quartiles of long chain omega-3 fatty acid intake (p=0.7 for trend), EPA (p=0.7 for trend) or DHA (p=0.9 for trend).	differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			status: DSM Dementia assessed by 3 step protocol: 1. Combined Mini-Mental State Examination (MMSE) and Geriatric Mental State Schedule (GMS) 2. Camdex examination for those with MMSE scores<26 or GMS scores>0 3. Evaluation by neurologist and neuropsychologist Final diagnosis made by panel consisting of neurologist, neuropsychologist and research physician according to DSM-III-R;NINCDS-ADRDA for AD **Informant interview?:** No		
Devore, Kang, Okereke, et al., 2009 Nurses Health	**Geographical location:** USA (participants dispersed across several states in the US)	**Age:** Mean (SD):74(2.3) **Sex:** Female: 1550 (100%) Male: 0 (0%)	**Risk factor/exposure 1:** Physical activity levels **Method of assessing risk factor/exposure 1:**	**1) Follow-up rate:** -1550 women analyzed for cognitive decline across 3 interviews over 4 yrs; >90% follow-up. **2) Important baseline differences:**	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Study Participants Physical activity levels and cognition in women with type 2 diabetes	**Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1550 **Duration of follow up:** 4 years **Time from risk factor assessment to final cognitive assessment:** 4 yrs	**Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-Demented **Inclusion criteria:** Nurses Health Study participants, aged≥70 with type 2 diabetes. (Nurses health study is a long-running study of registered nurses that started in 1976 with recruitment of 121,700 nurses between ages 30-55yrs) **Exclusion criteria:** -Women unable to walk -Women diagnosed with Parkinson's or Alzheimer's disease prior to initial cognitive assessment -Women who did not report information on specific disability indicators (15%) (osteoarthritis, chronic bronchitis, fatigue, balance problems, moderate-to-severe body pain, and limitations in walking)	Self-report: Self reports of physical activity converted into metabolical equivalent hours per week (MET-hr) (e.g. MET for sitting=1, for running =12, for stair climbing=8 and so on) MET multiplied by hours per activity and summed over all activities gives energy expenditure per week.) based on average of 5 reports over a median of 13.3 years **Covariates/potential confounders adjusted for in analyses:** Age, education, baseline cognitive status, disability indicators (osteoarthritis, chronic bronchitis, fatigue, balance problems, moderate-to-severe body pain, and limitations in walking) **Method(s) of assessing cognitive status:** Battery of 6 cognitive tests administered by trained nurses via telephone; starting with telephone interview of	Differences in self-reported physical disability across increasing tertiles of physical activity **3) Outcome of interest #1** Mean difference in change in cognitive function scores by tertile of average physical activity Adjusted for age, education and baseline cognitive status, women with greater levels of long-term physical activity associated with less cognitive decline on TICS, global and verbal cognition; however this finding was not statistically significant when adjusted for disability indicators.	2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			cognitive status (TICS) and including, East Boston Memory Test-immediate and delayed recall, Category Fluency, delayed recall of 10 word list and digit span backward. Assessment expressed in terms of general cognition and verbal memory; general cognition obtained by averaging all 6 tests; verbal memory score obtained by averaging 4 tests: immediate and delayed recalls of East Boston Memory Test and Telephone interview of Cognitive Status 10-word list. Baseline interview followed by 3 interviews over a 4 year period. **Informant interview?:** No		
Dik, Jonker, Bouter, et al., 2000 LASA study	**Geographical location:** Amsterdam, The Netherlands **Setting:** LASA: Community	**Age:** Mean (SD): Equal numbers in 5 year intervals from 55 to 85. Only subjects >62 in this study.	**Risk factor/exposure 1:** APOE E4 genotype **Method of assessing risk factor/exposure 1:** genotyping	**1) Follow-up rate:** 876/1243 = 70.5% Death 13.5%; refusal 11.1%; frailty 4.4%; loss of contact 0.5%. 22 subjects lost data leaving 854 with testing at both time points. Loss to follow-up was associated	**Comments:** APOE E4 is a risk factor for memory decline only in cognitively impaired individuals (MMSE 21-26), not in cognitively normal subjects (MMSE ≤27). Cognitively impaired subjects with APOE E4 who are >75 years of age are at particularly

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Study design: Prospective cohort **Number of participants enrolled:** LASA: 3107 enrolled. 1551provided blood. 1297 genotypes; Excluded 54 excluded because MMSE <21. Total 1243 participated **Duration of follow up:** LASA: mean of 3.1 years **Time from risk factor assessment to final cognitive assessment:** Average 3.1 years (SD 0.2)	**Range:** ≥62 to 85 **Sex:** [n (%)] Female: Male: **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age ≥62 MMSE ≥21 **Exclusion criteria:**	**Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level E4 carriers E4 noncarriers MMSE 27-30 (normal cognition) MMSE 21-26 (impaired cognition) **Method(s) of assessing cognitive status:** MMSE; AVLT (3 trials); memory decline was defined as ≥1 SD mean change score on IR, DR and retention based on AVLT. **Informant interview?:** No	with older age, lower education and lower scores on all cognitive measures (p<.001). No association between follow-up and APOE genotype. **Important baseline differences:** NR **Outcome of interest #1** APOE E4 is a risk factor for memory decline only in cognitively impaired individuals (MMSE 21-26), not in cognitively normal subjects (MMSE ≤27). In Subjects with MMSE 21-26 And APOE E4 (adjusted for age, sex, education and baseline recall scores) OR decline on IR 3.8 (95% CI 1.4-10) OR decline on DR 2.9 (1.2-7.0) OR decline on retention 3.3 (1.1-10.1). No association of decline in cognitively normal subjects with APOE E4. **Outcome of interest #2** Subjects with MMSE 21-26 and age >75 and APOE E4 OR decline on IR 4.5 (1.4-13.8) OR decline on DR 3.6 (1.2-10.8) OR decline on retention 6.6 (1.5-29.7)	increased risk for decline. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Yes 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the cohort: Yes 5) Validated method for ascertaining exposure: Yes 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Yes 9) Completeness of follow-up: Partial 10) Analysis controls for confounding: Yes 11) Analytic methods appropriate: Yes
Dodge, Zitzelberger, Oken, et al., 2008	**Geographical location:** Oregon, US	**Age:** Mean (SD): 87.5 yr (2.14-2.22) Range: 85-94.1 yrs	**Risk factor/exposure 1:** RCT – Ginkgo biloba extract	**1) Follow-up rate:** 79/118 (66.9%) **2) Important baseline differences:**	**Comments:** Used proportional hazards models. Appeared to include everyone until the point of drop out (death, drop-out

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Setting: [Community – mailing to age-eligible in community and research in university aging and AD center **Study design:** RCT **Test intervention:** Standardized GBE (80 mg 3x daily) **Comparator intervention(s):** placebo **Number of participants enrolled:** 118 **Duration of follow up:** 42 mo **Time from risk factor assessment to final cognitive assessment:** 42 mo was the aim – in reality ave 3.0 (0.98) yr for placebo and 3.3 (0.77) yr for GBE	**Sex:** [n (%)] Female: 71 (60% Male: 47 (40%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Normal **Inclusion criteria:** Age > 84 yrs; no subjective complaint of memory impairment compared to others of their own age; has not sought assessment for memory or cognitive dysfunction; normal memory function defined by an education adjusted score on the Logical Memory Subscale of the Wechsler Memory Scale-Revised; Mini0Mental State Examination score >23; Blessed Orientation Memory Concentration Test <12; Functionally independent (ADL=0); Clinical Dementia Rating = 0; Absence of significant depressive symptoms (CES-D-10 score <4); Sufficient vision and hearling to	**Method of assessing risk factor/exposure 1:** Direct measurement of number of pills taken **Covariates/potential confounders adjusted for in analyses:** Covariates used in secondary analyses Age Sex Educational level Baseline MMSE score Adherence to intervention medication Depression APOE # prescriptions Cumulative illness scale Living arrangement **Method(s) of assessing cognitive status:** Other – change in CDR from 0.0 to 0.5 Some analyses examined decline in delayed recall task – but description of these results are not clear **Informant interview?:** Yes	None **3) Outcome of interest #1** In unadjusted model, no difference in conversion to CDR = 0.5 for GBE vs placebo group. **4) Outcome of interest #2** When adjust for adherence to intervention, GBE group at lower risk of converting to CDR = 0.5. Effect remains when all other covariates added. **5) Outcome of interest #3** GBE does not have an effect on delayed recall test over time (not sure if this is change in score or what)	due to stroke etc). This may account for some bias created by the ~30% attrition? **Quality assessment:** *For RCTs:* 1) Baseline comparability?: Yes 2) Valid AD/cognitive outcomes assessment?: Yes 3) Subjects/providers blind?: Yes 4) Outcome assessors blind?: Yes 5) Incomplete data adequately addressed?: No 6) Differential dropout rate < 10%?:No, closer to 12% 7) Overall dropout rate < 30%?: No 30-35% 8) Conflict of interest reported and insignificant?: Can't Tell, funding source not given, does state source of drug 9) Randomization adequate?: No, statistically matched 10) Allocation concealment adequate?: Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		complete all testing; sufficient English language skills to complete all testing; general health status that will not interfere with ability to complete longitudinal study; informant available with frequent contact with subject to verify functional status **Exclusion criteria:** Diseases associated with dementia such as AD, ischemic vascular dementia, normal pressure hydrocephalus, or Parkinson disease; significant disease of the CNS such as brain tumor, seizure disorder, subdural hematoma, cranial arteritis; current (within last 2 yrs) alcohol or substance abuse according to DSM-IV criteria; abnormal laboratory values indicating B12 deficiency, thyroid disease, or urinary tract infection (documented chronic bacterial colonization is acceptable); unstable or significantly symptomatic			

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		cardiovascular disease such as CAD with frequent angina, or CHF with shortness of breath at rest; insulin dependent diabetes mellitus; active systemic CA within 5 yrs of study entry (Gleason Grade <3 prostate CA, and non-metastatic skin CA are acceptable); illness that requires >1 visit per mo to clinician; progressive vision loss; need for oxygen supplementation for adequate function; frequent use of high doses of analgesics; sedative medications except for those used occasionally for sleep; subjects taking CNS-active medications that have not been on stable doses for at least 2 mos including cimetidine, beta-blockers, and selective serotonin reuptake inhibitors; subjects taking neuroleptics, antiparkinsonian agents, systemic corticosteroids, and narcotic analgesics; Subjects will NOT be excluded if they are taking other over-the-			

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		counter supplements, but the dose must not be changed during the course of the trial unless medically indicated; Subjects taking cholinesterase inhibitors; use of investigational drugs within 5 half-lives prior to baseline			
Doody, Ferris, Salloway, et al., 2009 *(Aricept)*	**Geographical location:** U.S.A, multicenter **Setting:** NR **Study design:** RCT with 3-week placebo run-in phase **Test Intervention:** Donepezil 5mg daily * 6 weeks, then 10mg daily **Comparator**:**Intervention:** Placebo **Number of participants enrolled:** 821 randomized; 778 analyzed **Duration of follow up:** years	**Age:** Mean (SD):70.2 (9.71), 69.8 (10.32) **Sex:** [n (%)] Female: 354 Male: 424 **Race/ethnicity:** [n (%)] Caucasian 676 (87%) **Baseline cognitive status:** Amnestic MCI **Inclusion criteria:** Age 45-90 Memory complaint corroborated by an informant MCI defined by: CDR 0.5 with memory box score 0.5 or 1.0 and <= 2 other boxes >=1; MMSE 24-28; Logical Memory II delayed Paragraph recall ≤ 8	**Covariates/potential confounders adjusted for in analyses:** [delete any from the list below that do not apply and add items as needed] Age Educational level **Method(s) of assessing cognitive outcomes:** [delete all that do not apply] Primary: Modified ADAS-Cog (0-89 point scale, 13 subtests) and CDR sum of boxes (0-18; 6 subscales each rated 0-3; CDR-SB) Secondary: MMSE Symbol Digit Modalities Test Digit Span Backwards	**1) Follow-up rate:** 499/821 randomized = 60.8% 499/778 analyzed = 64.1% Mean exposure rate to treatment Donepezil = 248 (120) days Placebo = 282 (100) days **2) Important baseline differences:** No, comparable at baseline **3) Outcome of interest #1** Analyzed by analysis of covariance using last observation carried forward (mean difference = (baseline – follow-up)donepezil – (baseline – follow-up)placebo ADAS-Cog: mean difference at f/u = -0.90 (SE 0.37), p=0.01 favoring donepezil CDR-SB, mean difference not given; no statistically significant difference **4) Outcome of interest #2** Mean change from baseline to endpoint on 8 cognitive measures	**Comments:** None **Quality assessment:** *For RCTs:* 1) Baseline comparability?: Yes 2) Valid AD/cognitive outcomes assessment?: Yes 3) Subject/providers blind?: Can't Tell; "double-blind" but who is blind is not described 4) Outcome assessors blind?: ?: Can't Tell; "double-blind" but who is blind is not described 5) Incomplete data adequately addressed?: No, used LOCF 6) Differential dropout rate ≤10%?: No 7) Overall dropout rate ≤30%?: No 8) Conflict of interest reported and insignificant?: Yes, funded by industry, investigators, including analysts employed by sponsor 9) Randomization adequate?: Yes 10) Allocation concealment adequate?: Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	48 weeks	(education ≥ 16 years), ≤ 4 (8-15 years educ), ≤ 2(≤ 7 years educ); modified Hachinski Ischemia scale score ≤ 4; an informant; brain imaging w/in 12 months without infarction or focal lesions. **Exclusion criteria:** Dementia Neurologic or psychiatri disorder Sleep disorder that could affect cognition Alcohol abuse/dependence w/in 5 years Uncontrolled HTN or DM Any other medical condition incompatible with study participation Past treatment with ChEI or memantine for > 1 month or within 3 months of study screening Concomitant anticholinergics, anticonvulsants, antiparkinsonian agents, stimulants, cholinergic agents, antipsychotics or antidepressants or anxiolytics with anticholinergic or procholinergic effects.	tst Pereived Deficits Questionnaire (PDQ) PDQ for relatives Neuropsychiatric Inventory Patient Global Assessment Clinical Global Impression of Change-Mild Congitive Impariement **Informant interview?:** No	Of 8 secondary measures, donepezil treated subjects showed statistically significant benefit on two: Perceived Deficits Questionnaire: -1.8 (0.8)donepezil vs. -0.2 (0.7) placebo Patient Global Assessment: 3.3 (0.1) donepezil vs. 3.5 (0.1) placebo **5) Outcome of interest #3** Discontinuation due to adverse event 72 (18.4%) donepezil vs. 32 (8.3%) placebo Any adverse event: 318 (81.3%) donepezil vs. 267 (69.0%) placebo; most common – diarrhea (16.4% vs. 3.4%), muscle spasms (13.3% vs. 1.8%) and nausea (9.7% vs. 4.4%) Serious adverse event: 48 (12.3%) donepezil vs. 41 (10.6%) placbo Deaths: 3 donepezil, (lymphoma, sudden death, lung cancer) 1 placebo (pleural mesothelioma) – all judged to be unrelated to study medication	

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
DuFouil, Alperovitch, Ducros, et al., 2003 **EVA**	**Geographical location:** Nantes, France **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1241 **Duration of follow up:** With a population of 1241 at baseline , 1151 followed up for 2 yrs, 986 for 3 years, 782 for four years OR for homocysteine calculated for 2 yr change in mmse **Time from risk factor assessment to final cognitive assessment:** blood drawn at baseline, cog testing each time subject returned.	**Age:** Mean (SD): 67 (3.0) Range: 61-73 **Sex:** [n (%)] Female: 58.6% Male: 41.4% **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** doesn't look like they eliminated the impaired but mean mmse high at baseline **Inclusion criteria:** Homocysteine measured at baseline 2 year f/u completed **Exclusion criteria:** NR	**Risk factor/exposure 1:** homocysteine Fasting plasma stored unkn length of time **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** age, gender, education, baseline cognition, bmi, etoh, smoking, htn, hyperchol, glycemic status, hx of vascular dz, folate, vit B12 concen. **Method(s) of assessing cognitive status:** change in test scores (MMSE, Trails B, Digit symbol substitution test, Finger tapping) **Informant interview?:** No	**1) Follow-up rate:** With a population of 1241 at baseline , 1151 followed up for 2 yrs, 986 for 3 years, 782 for four years 1107/1241 (89%) in cognitive decline analysis **2) Important baseline differences:** In the higher class of hcy, subjects were older, more men, more ETOH, and more likely to have htn, dm, and lower folate levels Overall, lower cognitive performance in those with higher homocysteine. **3) Outcome of interest #1** cognitive deterioration defined as mmse decrease of 3 or more pts in two years (118 out of 1107 with 2 year f/u). OR 2.8 (1.2 – 6.2) for highest hcy group (>15 umol/l) vs lowest hcy group (<10 umol/l) Stratified analysis by HTN, B12, folate, h/o vascular disease, glycemic status, and cholesterol status did not show any interaction between these factors and homocysteine. **4) Outcome of interest #2** Change in cognition evaluated as a continuous measure. Statistically significant greater decline on 3 of 4 outcomes (MMSE, Finger tapping, DSST) for highest homocysteine vs. lowest. Comparison of 2nd and 3rd	**Comments:** Question 2 Population was 61-73 years old at baseline and likely included some impaired subjects but baseline mmse was 27.6 with a mean age of 67 (3.0) Appears that homocysteine categories determined post-hoc based on data and not based on theorectical or a priori thresholds **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial, MMSE decline of 3 points of unknown clinical significance 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				highest homocysteine vs lowest groups did not show a statistically significant difference.	
Dufoil, Fuhrer, Dartigues, et al., 1996 PAQUID Study	**Geographical location:** Gironde, France **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2792 overall; 2726 in this analysis **Duration of follow up:** 3 years **Time from risk factor assessment to final cognitive assessment:** 3 years	**Age:** Range: ≥65 years **Sex:** [n (%)] Female: 1632 (59.9%) Male: 1094 (40.1%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age >=65 Cognitive assessment at baseline and follow-up **Exclusion criteria:** Dementia	**Risk factor/exposure 1:** Depression (CESD >16 for men and >22 women) **Method of assessing risk factor/exposure 1:** Self-report at baseline and 3 year f/u **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Marital status IADL Baseline cognition **Method(s) of assessing cognitive status:** MMSE decline >= 5 points **Informant interview?:** No	**1) Follow-up rate:** 1600 of 2726 (59%); 800 refused, 311 died, and 15 lost to follow-up **2) Important baseline differences:** Not given Logistic Regression Analysis **3) Outcome of interest #1** Incidence of cognitive impairment defined by MMSE decline >=5 points. (48 subjects) CESD > threshold at baseline; OR 0.8 (95% CI 0.3 to 2.1) Sensitivity analysis to evaluate the effects of subjects lost to follow-up showed no association between depressive symptom and cognitive impairment until assuming a 10% rate of cognitive impairment in depressive non-respondents (compared to an observed rate of 2.8% in depressed respondents) **4) Outcome of interest #2** Change in MMSE (F/U – Baseline) was associated with change in CESD scores; adjusted estimate Beta=-0.026 (95%CI -0.039 to -0.013) **5) Outcome of interest #3** Mean change +0.3 (2.6)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Yes 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the cohort: Yes 5) Validated method for ascertaining exposure: Yes 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Can't Tell 9) Completeness of follow-up: No 10) Analysis controls for confounding: Yes 11) Analytic methods appropriate: Yes
Dullemeijer, Durga,	**Geographical location:**	**Age:** Mean (SD): 60 (6.0)	**Risk factor/exposure 1:**	**1) Follow-up rate:** 404/408 (2 that did not return for fup	**Comments:** Question 2

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Brouwer, et al., 2007 FACIT	Wageningen, Netherlands **Setting:** NR **Study design:** Secondary analyses of an RCT arm **Number of participants enrolled:** 404 subjects in this analyses **Duration of follow up:** 3 yrs **Time from risk factor assessment to final cognitive assessment:** 3 yr	**Sex:** [n (%)] Female: 117 (29) Male: 287 (71) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented (assume because part of RCT and also young age of sample) **Inclusion criteria:** Participants in FACIT, a randomized placebo-controlled trial of folic acid supplementation on cognitive performance, carotid intima-media thickness, and hearing. Men and postmenopausal women aged 50-70 Plasma total homocysteine concentrations:≥ 13 micromol/L and ≤ 26 micromol/L and serum vitamin B-12 concentrations ≥ 200 pmol/L. **Exclusion criteria:** NR	n-3 fatty acid **Method of assessing risk factor/exposure 1:** Direct measurement **Method of assessing risk factor/exposure 2:** Self-report Proxy report Direct measurement Medical record Other **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status Erythrocyte folate ETOH use **Method(s) of assessing cognitive status:** Other – used standardized test scores at baseline and 3 yr follow-up in 5 domains **Informant interview?:** No	had died**)** **2) Important baseline differences:** NR by exposure group **3) Outcome of interest #1** Higher plasma n-3 PUFAs predicted less decline over 3 yr in domains of sensorimotor speed (p = 0.02) and complex speed (<0.01), but domains of memory, information processing speed, and word fluency showed no sig association with n-3 PUFAs	This paper has a nice table (Table 5) of other longitudinal studies assessing n-3 PUFAs. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Engelhart, Geerlings, Ruitenberg, et al., 2002 Rotterdam Study	**Geographical location:** Rotterdam, Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 5395 **Duration of follow up:** Mean 6 yr **Time from risk factor assessment to final cognitive assessment:** Mean 6 yr	**Age:** Mean (SD): 67.7 (7.8) **Sex:** [n (%)] Female: 3183 (59) Male: 2212 (41) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 55 yr; resident of specific suburb in Rotterdam, had reliable nutritional data, not demented at baseline **Exclusion criteria:** Nursing home residents	**Risk factor/exposure 1:** anti-oxidant intake **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status ETOH use Smoking BMI Total energy intake Presence of carotid plaques Supplemental antioxidant use **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes	**1) Follow-up rate:** authors note f/u for dementia was 99.9% - but there were exclusions from analytical sample for other reasons—can not determine overall f/u – but in general appears to be adequate **2) Important baseline differences:** NR **3) Outcome of interest #1** Fully adjusted model, Vit C associated with reduced risk of incident AD (RR-0.82; 0.68-0.99) **4) Outcome of interest #2** Fully adjusted model, Vit E borderline association with reduced risk of incident AD (RR-0.82; 0.66-1.00) **5) Outcome of interest #3** Fully adjusted model, beta carotene (RR-0.87; 0.70-1.09) and flavonoids (RR-0.99; 0.83-1.18) not associated with reduced risk of incident AD	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: No 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Evans, Hebert,	**Geographical location:**	**Age:** Mean (SD): NR	**Risk factor/exposure 1:**	**1) Follow-up rate:** Initial prevalence study of 3623	**Comments:** None

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Beckett, et al., 1997 NIA EPESE study (Established Populations for Epidemiologic Studies of the Elderly)	East Boston, MA **Setting** Community **Study design** Prospective cohort **Number of participants enrolled:** 642 enrolled. This number was a stratified random sample drawn from a cohort of **Duration of follow up:** 4.3 years **Time from risk factor assessment to final cognitive assessment:** 4.3 years	Range:65 -80+ years **Sex:** Female:362(56.4%) Male: 280(43.6%) **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** 65+ years old, non-demented, community resident. **Exclusion criteria:** NR	years of formal schooling **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2** Level of occupational status **Method of assessing risk factor/exposure 2:** Self-report "Occupations were coded according to perceived prestige." **Covariates/potential confounders adjusted for in analyses** Age Sex F/u interval For combined logistic regression model, Occupational prestige score and income were also included. **Method(s) of assessing cognitive status** All participants underwent clinical	residents. 2313 free of AD. Excluded 177 with poor or intermediate memory performance. Sample = 2136 303 died, 409 did not participate. Stratified random sample of 642 of remaining 1601 persons (79.6%) in analytical sample. **2) Important baseline differences:** NA **3) Outcome of interest #1—probable AD** 95 with incident probably AD. Fewer years of education (OR 0.83; 95% CI: 0.75, 0.92), lower occupation prestige (OR 0.96, 95% CI: 0.93,0.99) and lower income are associated with increased risk of probable AD In the logistic regression analysis of risk of incident clinically diagnosed AD, odds ratio compared to the rest of the population was 0.85 (0.75-0.95).	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			evaluation. NINCDS-ADRDA **Informant interview** No		
Everson-Rose, Mendes de Leon, Bienias, et al., 2003 Chicago Health and Aging Project (CHAP)	**Geographical location:** Chicago, IL **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 4398 **Duration of follow up:** Mean: 5.3 yrs **Time from risk factor assessment to final cognitive assessment:** Mean: 5.3 yrs	**Age:** Mean (SD): 73.9 (6.4) **Sex:** Female: 2731 (62.1%) Male: 1667 (37.9%) **Race/ethnicity:** Black: 2713 (61.7%) Non-Black: 1685 (38.3%) **Baseline cognitive status:** NR. No exclusion for dementia. **Inclusion criteria:** In CHAP study. Age ≥65 yrs, living in south side of Chicago. Must have had tests of cognitive function from at least 2 of 3 interviews. **Exclusion criteria:** NR	**Risk factor/exposure 1:** Socieconomic position (SEP). **Method of assessing risk factor/exposure 1:** Self-report. Composite index: parental educational attainment and occupational prestige and self-reported family financial status as a child. **Risk factor/exposure 2:** Childhood cognitive milieu. **Method of assessing risk factor/exposure 2:** Self-report. Composite index of 3 questionnaires: frequency of someone in household having been read to, told stories to, or played games with as a child.	**1) Follow-up rate:** 6158 in CHAP study. 1175 died before f/u, 149 relocated, 341 refused, 34 could not be contracted, and 61 were missing for other reasons. 4398 in this study (71.4% of eligible) **2) Important baseline differences:** NA **3) Outcome of interest #1** SEP: Each 1-unit increase in childhood SEP associated with a 0.158-standard unit higher level of cognitive function (95% CI: 0.130, 0.186, p<0.0001). **4) Outcome of interest #2** Cognitive milieu: Each 1-unit increase in childhood SEP associated with a 0.055-standard unit higher level of cognitive function (95% CI: 0.039 ,0.070, p<0.0001). **5) Outcome of interest #3** Neither SEP (β = -0.003, 95% CI: -0.009, 0.003; p=0.32) nor cognitive milieu (β==-0.001, 95% CI: -0.004, 0.002, p=0.39) was associated with cognitive change over time.	**Comments:** None. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Partial, conceptually sensible but no citation for validity. 6) Validated method for ascertaining clinical outcomes?: Yes. 7) Outcome assessment blind to exposure?: Can't Ttell. 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Covariates/potential confounders adjusted for in analyses: Age Race Sex Educational level Interactions of time with childhood **Method(s) of assessing cognitive status:** Global cognitive index, derived from measures of memory, perceptual speed. Symbol Digit Modalities Test; recall portions of the East Boston Story; MMSE. **Informant interview?:** No		
Feart, Samieri, Rondeau, et al., 2009 Three-City (3C) study	**Geographical location:** Bordeaux, France **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1524 enrolled;	**Age:** Mean (SD): 75.9 Range:67.7-94.9 **Sex:** [n (%)] Female: 883,62.6% Male: 527,37.4% **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:**	**Risk factor/exposure 1:** Mediterranean Diet **Method of assessing risk factor/exposure 1:** Self-report; Based on food frequency questionnaire administered by a specifically trained	**1) Follow-up rate:** 1213/1524= 79.6% 1524 enrolled; 1410 participants without dementia had at least 1 follow-up; 1213 participants examined at the end of the 3rd and final follow-up exam. **2) Important baseline differences:** Greater Mediterranean diet adherence was associated with male	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Yes, 45% power to detect HR of 0.6

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	1410 analyzed **Duration of follow up:** 7 years **Time from risk factor assessment to final cognitive assessment:** 7 years	Non-demented **Inclusion criteria:** -65 years or older **Exclusion criteria:** -Dementia at baseline	dietician, frequency of consumption of 40 categories of food and beverages for all meals were recorded and food groups considered to be part of Mediterranean diet were identified and adherence to the diet rated on a 0 to 9 scale. **Covariates/potential confounders adjusted for in analyses:** Age, Sex, Education, Marital Status, Energy Intake, Physical Activity, Depressive symptomatology, Taking 5 medications or more, Apolipoprotein E genotype, Cardiovascular risk factors, Stroke **Method(s) of assessing cognitive status:** DSM 4 neuropsychological tests administered by trained psychologists: 1. Mini Mental State	sex and being married but not with education, income or physical activity Individuals in the middle or high Mediterranean diet score categories had a lower mean BMI and higher mean energy intake than those in the lowest category **3) Outcome of interest #1** Main outcome measure was cognitive performance on the 4 neuropsychological tests. Higher Mediterranean diet score associated with fewer MMSE errors (β=-0.006; 95%CI, -0.01 to -0.0003; P=0.04 for 1 point of the Mediterranean diet score) and therefore slower MMSE cognitive decline but this was not consistently the case with other cognitive tests. Among the subgroup who did not develop dementia, higher Mediterranean diet score associated with fewer MMSE errors and less decline on the FCSRT **4) Outcome of interest #2** 99 incident cases of dementia 66 probable or possible cases of Alzheimer disease High Mediterranean diet score (6-9) HR 1.12 (0.60-2.10) nor middle scores (4-5) HR 1.11 (0.63-1.94) compared to low scores (0-3) were not associated with lower rates of dementia. High Mediterranean diet score (6-9)	4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Examination (MMSE) 2. Isaacs Set Test (IST) 3. Benton Visual Retention Test (BVRT) 4. Free and Cued Selective Reminding Test (FCSRT) Diagnosis of dementia based on 2 Stage procedure **First stage:** Neurological exam by a neurologist **Second stage:** Review of potential cases of dementia by independent committee of neurologists with in depth assessment of medical history of each participant to obtain consensus on diagnosis and etiology according to criteria of the Diagnostic and Statistical Manual of Mental Disorders. **Informant interview?:** No	HR 0.86 (0.39-1.88) nor middle scores (4-5) HR 0.99 (0.51-1.94) compared to low scores (0-3) were not associated with lower rates of AD.	
Fillenbaum, Kuchibhatla, Hanlon, et al., 2005 Subset of	**Geographical location:** Durham, Granville, Vance, Warren, & Franklin Counties, NC **Setting:**	**Age:** Mean (SD): 73 Range: 65 - 105 **Sex:** [n (%)] Female: 382 (62%) Male: 234 (38%)	**Risk factor/exposure 1:** Vitamins C and E **Method of assessing risk factor/exposure 1:**	**1) Follow-up rate:** NR **2) Important baseline differences:** Differed on age, education, health service use, prescription drugs	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE) Study	Community **Study design:** Prospective cohort **Number of participants enrolled:** 616 **Duration of follow up:** Follow-up ranged from 3 – 10 years for incident dementia **Time from risk factor assessment to final cognitive assessment:** 3-4 yrs (data used from the wave prior to the diagnosis of dementia – assume meant in-person wave)	**Race/ethnicity:** [n (%)] African-American 382 (62%) Other 234 (38%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 yo; participating in the Duke EPESE Study **Exclusion criteria:** The implication seems to be that the potential subjects were chosen to oversample for blacks and then all selected subjects in the community were taken.	Self-report Proxy report **Covariates/potential confounders adjusted for in analyses:** Age Educational level Marital status Income Functional status Health services use # prescription drugs time frame of exposure to vitamins **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes – does not actually say, but the CERAD protocol (which was used) does use an informant	**3) Outcome of interest #1** Vitamin E use at baseline or at wave prior to dementia diagnosis not associated with incident AD **4) Outcome of interest #2** Vitamin C use at baseline or at wave prior to dementia diagnosis not associated with incident AD	2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes. 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Can't Tell 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Fitzpatrick, Kuller, Lopez, et al., 2009 Cardiovascular Health Study	**Geographical location:** Forsyth County, NC; Washington County, MD; Sacramento County, CA; Pittsburgh, PA **Setting:** Community	**Age:** Mean (SD): 74.7 **Sex:** [n (%)] Female: 1654 (59.1%) Male: 1144 (40.9%) **Race/ethnicity:** [n (%)] White 2457 (87.8%) Non-white 341 (12.2%)	**Risk factor/exposure 1:** BMI at mid and late life **Method of assessing risk factor/exposure 1:** Self-report at midlife and Direct measurement at	**1) Follow-up rate:** Not clearly stated. Subjects with dementia and mild cognitive impairment excluded from population. **2) Important baseline differences:** ≤.001 for age, sex, race, education, smoking status, diabetes mellitus, hypertension, ABI, CRP and IL-6	**Comments:** Question 1 In evaluations of midlife obesity, an increased risk of dementia was found for obese (BMI _30) vs normal-weight(BMI20-25) persons, adjusted for demographics (hazard ratio [HR], 1.39; 95% confidence interval [CI], 1.03-1.87) and for cardiovascular risk factors (1.36;

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			late life	levels.	0.94-1.95).The risk estimates were reversed in assessments of late-life BMI. Underweight persons (BMI _20) had an increased risk of dementia (1.62; 1.02-2.64), whereas being overweight (BMI_25-30) was not associated (0.92; 0.72-1.18) and being obese reduced the risk of dementia (0.63; 0.44-0.91) compared with those with normal BMI.
	Study design: Prospective cohort **Number of participants enrolled:** 2798 **Duration of follow up:** 5.4 years **Time from risk factor assessment to final cognitive assessment:** mean 5.4 years	**Baseline cognitive status:** Normal Non-demented **Inclusion criteria:** Medicare recipients ≥65 years of age in target counties. **Exclusion criteria:** Dementia or mild cognitive impairment	**Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status cardiovascular and dementia risk factors (including history of hypertension, diabetes mellitus status, coronary heart disease, total cholesterol level, ankle-arm index, C-reactive protein level, interleukin 6 level, smoking status, kilocalories expended per week, and apolipoprotein E genotype**)** **Method(s) of assessing cognitive status:** NINCDS-ADRDA modifiedMMSE,Digit Symbol Substitution Test,BentonVisual Retention Test, TrailsAandB, Center for Epidemiologic Studies Depression Scale, medications	**3) Outcome of interest #1** Classification resulted in 480 persons with incident dementia,245with Alzheimer disease (no vascular dementia), and 213 with vascular dementia (with or without Alzheimer disease). BMI measured at Midlife (age 50) adjusted HR Overall 1.0 (0.95-1.04) Underweight 1.47 (0.7-3.09 Normal- reference Overweight 1.04 (0.74-1.47) Obese 1.25 (0.74-2.11) **4) Outcome of interest #2** BMI measured at late life (age 65 or older) adjusted HR Overall 0.95 (0.74-0.99) p=.008 Underweight 1.42 (0.74-2.70) Normal- reference Overweight 0.74 (0.52-1.05) Obese 0.58 (0.31-.96) p=.03	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			inventory, activities of daily living, instrumental activities of daily living, other physical function measures (gait speed, balance tests, grip strength, etc), and documentation of hospitalized medical events **Informant interview?:** no. except for deceased.		
Fotuhi, Zandi, Hayden, et al., 2008 Subset of Cache County Study	**Geographical location:** Cache Country, UT **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3376 **Duration of follow up:** f/up 3 and 8 years. At least one f/u to get into study **Time from risk factor assessment to final cognitive assessment:** Ranged generally from	**Age:** Mean (SD): Grp 1 – 74.3 (6.6) Grp 2 – 73.9 (6.3) Grp 3 – 73.6 (5.5) Grp 4 – 73.4 (6.1) Grp 5 – 72.9 (6.1) **Sex:** [n (%)] Female: 1974 (58.4%) Male: 1402 (41.6%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 yo; resident of Cache Country, UT **Exclusion criteria:**	**Risk factor/exposure 1:** nsaids **Method of assessing risk factor/exposure 1:** self report, probe questions, pill bottles **Risk factor/exposure 2:** vit E, vit C **Method of assessing risk factor/exposure 2: :** self report, probe questions, pill bottles **Covariates/potential confounders adjusted for in analyses:**	**1) Follow-up rate:** three waves, 63% and 37% **2) Important baseline differences:** more females using vit E, vit C or nsaids, vit E and C users more likely to have E4 **3) Outcome of interest #1** Users of all 3 (nsaids, vit e, vit c) had less decline than nonusers, but only significant in E4 carriers. **4) Outcome of interest #2** Users of vits e and c performed better at baseline as did users of nsaids alone, but only the combined users did better over time.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	3 to 8 years	Dementia @ baseline; only one 3MS evaluation; incomplete info on medication use	Age Sex Educational level Dm, cva, apoE status **Method(s) of assessing cognitive status:** change in 3MS score **Informant interview?:** No		confounding?: Yes 11) Analytic methods appropriate?: Yes.
Fratiglioni, Wang, Ericsson, et al., 2000 Kungsholmen Project	**Geographical location:** Kungsholmen district in Stockholm, Sweden **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1473 **Duration of follow up:** 3 yrs **Time from risk factor assessment to final cognitive assessment:** 3 yrs	**Age:** Range: >75 **Sex:** [n (%)] Female: 338 (35%) Male: 897 (65%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Not demented, Lived at home, Good cognition (Mini Mental Status Examination [MMSE]>23) >75 yrs of age Resident of Kungsholmen **Exclusion criteria:** NR	**Risk factor/exposure 1:** social network **Method of assessing risk factor/exposure 1:** Self-report and Proxy report (nurse interviews) **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status Physical function (ADLs) Depression Vascular disease **Method(s) of assessing cognitive**	**1) Follow-up rate:** Of the 1473s, 98 were excluded at baseline due to impaired cognition (MMSE<24) or institutionalization, and 172 refused to participate in the follow-up examination. Analytical sample = 1203. Follow up rate: 87.5% **2) Important baseline differences:** In comparison with the participants, the dropouts were younger (odds ratio 0·96, p=0·017). Differences in social network characteristics not reported. **3) Outcome of interest #1** 176 incident dementia cases (126 of Alzheimer's disease and 32 vascular dementia) Adjusted RR compared with those who were married and living with someone RR(95% CI): Single and living alone 1·9 (1·2–3·1)	**Comments:** Question1 Results for vascular and AD presented together though most dementia is diagnosed as AD. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?:

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			status: DSM **Informant interview?:** Yes, only when participant was unable to answer	Widowed/divorced and living alone 1·5 (0·9–2·2) Married and living alone 1·5 (0·4–6·4) Single and living with someone 1·4 (0·5–3·9) Widowed/divorced and living with someone 1·4 (0·4–4·7) **4) Outcome of interest #2** Adjusted RR compared to those who had daily to weekly contact with children and were satisfied: Contact less frequent than weekly and satisfying 1·3 (0·7–2·7) Contact less frequent than weekly and not satisfying 0·9 (0·4–2·3) Contact daily to weekly and not satisfying 2·0 (1·2–3·4) No children 1·4 (1·0–1·9) **5) Outcome of interest #3** RR compared to those who had close social ties on a daily to weekly basis with which they were satisfied: Contact less frequent than weekly and satisfying 1·1 (0·7–1·8) Contact less frequent than weekly and not satisfying 1·2 (0·7–2·0) Contact daily to weekly and not satisfying 1·4 (0·8–2·3) No friends or relatives 1·6 (1·0–2·6) All three social network variables were combined to construct a summary score. Compared to those with an extensive or moderate social network, those with a poor or limited social network were more likely to become demented (RR=1.6; 95%	Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				CI: 1·2–2·1).	
Freitag, Peila, Masaki, et al., 2006 Honolulu-Asia Aging Study (HAAS)	**Geographical location:** Oahu, Hawaii, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2505 **Duration of follow up:** 5.1 years of cognitive follow up. **Time from risk factor assessment to final cognitive assessment:** bp's checked 3 times 1965-1974, cognitive evals done 1991, 1994, 1999	**Age:** Mean at first assessment of dementia: 76.9 years **Sex:** Female: 0% Male: 100% **Race/ethnicity:** Japanese-American 100% **Baseline cognitive status:** Non-demented **Inclusion criteria:** Japanese-American Male Born between 1900 and 1919 Living on Oahu **Exclusion criteria:** NR	**Risk factor/exposure 1:** bp, (also pulse pressue, map **Method of assessing risk factor/exposure 1:** Direct measurement 3 times, five minutes apart, left arm while seated. **Covariates/potential confounders adjusted for in analyses:** age, education, apo E, antihypertensive meds, midlife alcohol, smoking and bmi, abi, hx of cad, cm or stroke at exam 4 (first cog assessment?) **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM CASI **Informant interview?:** Yes	**1) Follow-up rate:** 84% and 90% of survivors at two follow up cognitive evaluations **2) Important baseline differences:** higher midlife pulse pressures associated with older age, lower education, lower CASI score, higher bmi and higher sbp and dbp **3) Outcome of interest #1** "in the age adjusted model, sbp, dbp and map, and not pulse pressure, were significantly associated with incident dementia" (but not in fully adjusted model) **4) Outcome of interest #2** After admusting for confounders, the association remained significant only for sbp with a HR of 1.77 (1.1-2.84) for sbp $\geq$140 compared with sbp < 120. **5) Outcome of interest #3** Among those never treated for htn: (above is whole sample), all 4 bp components were correlated with incident dementia, an assoc that did not change after adjusting for cardiovasc confounders. HR 2.66 (1.51 – 4.68) for sbp $\geq$ 140 as compared to < 120. Only AD specific analysis reported - when the single bp component analyses were done (with only adj for age) the "results were similar for VaD	**Comments:** Analyses done for nonspecific dementia, that included148 cases of AD. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				and AD cases." Also of interest: "none of the analyses were significant when we performed them on late-life instead of midlife bp components"	
Gallacher, Bayer, Fish, et al., 2009 Caerphilly Study	**Geographical location:** UK **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2398 in parent study; 1160 analyzed and 982 with complete covariate data **Duration of follow up:** Mean 17.3 (1.3) years **Time from risk factor assessment to final cognitive assessment:** Mean 17.3 years	**Age:** Range: 48-67 at enrollment; **Sex:** [n (%)] Female: 0, 0% Male: 1160, 100% **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Men **Exclusion criteria:** NR	**Risk factor/exposure 1:** Anxiety: 20-item trait scale of the State Trait Anxiety Inventory (STAI); dichotomized at score of 31 ($\geq 31^{st}$ percentile) **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Educational level Marital status Alcohol consumption National Adult Reading test for cognitive function Vascular risk factors **Method(s) of assessing cognitive status:** 2-stage assessment; dementia using DSM,	**1) Follow-up rate:** 1160/2358 with baseline anxiety scores (49%) **2) Important baseline differences:** Multiple differences for those with low vs. high anxiety: social class, education, current smoker, GHQ30 score Also multiple differences between analytic sample and overall cohort. **3) Outcome of interest #1** Of total sample (1160), 69 had incident dementia and 174 CIND. OR for dementia/CIND with STAI in 31^{st} to 95^{th} percentile OR 2.19 (95% CI 1.24-3.88). Sensitivity analysis excluding men with some decline at baseline, OR 3.36 (1.61,7.01) **4) Outcome of interest #2** OR for CIND with STAI in 31^{st} to 95^{th} percentile OR 2.31 (95% CI 1.20-4.44). Sensitivity analysis excluding men with some decline at baseline, OR 3.32 (1.51,7.31)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Can't Tell 2) Selection minimizes baseline differences in prognostic factors?: Can't Tell 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial, assessment for CIND incomplete 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			CIND using CAMCOG <83 or CAMCG decline of ≥ 10 points or unable to produce a CAMCOG despite an attempt but without functional impairment or dementia **Informant interview?:** No		
Gatz, Tyas, St John, et al., 2005 Manitoba study of health and aging	**Geographical location:** Manitoba, Canada **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 766 **Duration of follow up:** 5 years **Time from risk factor assessment to final cognitive assessment:** 5 years	**Age:** Mean (SD): 74.5 (6.0) Range: 65 - 96 **Sex:** (%) Female: 473 (61.7%) Male: 293 (38.3%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented - >77 on 3MS **Inclusion criteria:** Age >=65 Randomly selected from those living at home in Manitoba Fluent – english or french **Exclusion criteria:** Life-threatening condition Unable to complete	**Risk factor/exposure 1:** Depression – Center for Epidemiological Studies Depression Questionnaire score ≥16 2. Participant reported history and duration of depression **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level **Method(s) of assessing cognitive status:** 2 –stage screening	**1) Follow-up rate:** NR Around 20% were lost to follow up due to death. **2) Important baseline differences:** NR **3) Outcome of interest #1** CESD>=16 OR for AD (36 cases) after 5 years f/u = 2.75 (95% CI 1.04 to 7.24) adjusted for age, sex, education Subject reported h/o depression was not associated with AD at 5 years; OR 1.50 (95% CI 0.49 to 4.63) Subject reported duration of depression was not associate with AD at 5 years; OR 1.01 (95% CI 0.88 to 1.15)	**Comments:** Mean education low at baseline 10.4 years (3.2) Subjects who died before f/u were older, had fewer years education and higher baseline CESD scores – could bias against an association. Analysis using logistic regression **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Yes 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the cohort: Partial 5) Validated method for ascertaining exposure: Partial 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		screen due to illness or sensory deficits	NINCDS-ADRDA **Informant interview?:** No		9) Completeness of follow-up: Can't Tell 10) Analysis controls for confounding: Yes 11) Analytic methods appropriate: No
Geda, Knopman, Mrazek, et al., 2006 Mayo Alzheimer Registry	**Geographical location:** Olmsted County, Minnesota **Setting:** Clinical **Study design:** Prospective cohort **Number of participants enrolled:** 840 **Duration of follow up:** 3.5 years **Time from risk factor assessment to final cognitive assessment:** NR	**Age:** Range: 50-102 **Sex:** [n (%)] Female: 519 (61.8) Male: 321 (38.2) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Normal **Inclusion criteria:** NR **Exclusion criteria:** Neurologic or psychiatic condition judged to interfere with cognitive assessment (including current depression) Psychiatric medicines that could compromise cognition	**Risk factor/exposure 1:** Depression; GDS (15 items) >= 6 before MCI diagnosis **2:** History of depression **Method of assessing risk factor/exposure 1:** Self-report every 12-18 months **2:** Clinical history-not specified **Risk factor/exposure 2:.** APOE Genotype **Method of assessing risk factor/exposure 2:** Direct: PCR using standard methods **Covariates/potential confounders adjusted for in analyses:** Age Educational level Sex	**1) Follow-up rate:** NR **2) Important baseline differences:** Depressed group older (mean of 84 vs. 77) and more female (68.5% vs. 60.4%) **3) Outcome of interest #1** MCI (50 cases) GDS >=6 (143 subjects) HR=2.2 (95% CI 1.2 to 4.1) Interaction between history of depression and GDS>=6 compared to referent group of no history and no current depression showed: HR = 4.5 (95% CI 1.9 to 10.9) for no h/o depression and GDS >=6 HR = 2.9 (95% CI 1.5 to 5.8) for h/o depression and GDS <6 HR = 2.6 (95% CI 1.1 to 6.3) for h/o depression and GDS >=6 Test for multiplicative interaction, p=0.008, antagonistic; additive interaction, p=0.3 Addtitional analysis showed: a non-significant increased risk for depressed men vs. women no "dose response" relationship when analyzing by depression severity (GDS scores) or duration of depressive symptoms significant interaction between	**Comments:** Mean duration of f/u less for depressed cohort (2.6 vs 3.5 years) Cox Proportional Hazards Model **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Yes 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the cohort: Partial (no race) 5) Validated method for ascertaining exposure: Partial (h/o depression not defined) 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure: Yes for APOE; Can't Tell for depression 8) Adequate follow-up period: Partial, depressive symptoms may be prodrome 9) Completeness of follow-up: Can't Tell 10) Analysis controls for confounding: Partial (no race) 11) Analytic methods appropriate: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Method(s) of assessing cognitive status: Clinical assessment, nuropsychological battery, MRI MCI by Petersen criteria (memory complaint, normal ADLs, normal general cognitive function, abnormal memory for age, not demented) **Informant interview?:** Yes	APOE genotype – increasing the HR for MCI	
Geerlings, den Heijer, Koudstaal, et al., 2008 Rotterdam Study	**Geographical location:** The Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 563 consented 486 analyzed **Duration of follow up:** 5.9 (1.6) years **Time from risk factor assessment to final cognitive assessment:**	**Age:** Range: 60 – 90 years **Sex:** [n (%)] Female: 238 (49%) Male: 248 (51%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age 60-90 Random selection stratified by age and sex **Exclusion criteria:** Dementia	**Risk factor/exposure 1:** History of Depression requiring the attention of a GP, psychologist or psychiatrist **2.** Current depression defined by CES >=16 **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive	**1) Follow-up rate:** 486/563 (86%) **2) Important baseline differences:** More women in depressed group **3) Outcome of interest #1** Risk of incident AD (33 cases) H/O depression, HR 2.46 (95% CI 1.15 to 5.26) CESD >=16 at baseline, HR1.02 (95% Ci 0.40 to .64) **Subgroup Analysis** H/O depression with onset before age 60 vs >=60 Early onset, 7 cases of AD, HR 3.70 (1.43 to 9.58) Late onset, 5 cases of AD, HR 1.71 (0.62 to 4.74) No h/o depression, 21 cases of AD, Reference group	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Yes 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the cohort: Partial 5) Validated method for ascertaining exposure: Partial, based on self-report 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	5.9 (1.6) years	Blind Contraindications to MRI	status Subjective memory complaint score **Method(s) of assessing cognitive status:** 2 stage evaluation; NINCDS-ADRDA **Informant interview?:** No		9) Completeness of follow-up: Yes 10) Analysis controls for confounding: Yes 11) Analytic methods appropriate: Yes
Glynn, Beckett, Hebert, et al., 1999	**Geographical location:** Boston, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3657 in overall cohort followed for up to 6 years Subsample 2068 age 65-81 with BP 9 years prior to cognitive baseline **Duration of follow up:** 6 years of cognitive assessments **Time from risk factor assessment to final cognitive**	**Age:** Mean (SD): 72.5 to 75.2 across BPgroups **Sex:** [n (%)] Female: 2230 (61%) Male: 1427 (39%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Not specified, but suspect many with cognitive impairment based on a mean of > 2 errors on SPMSQ **Inclusion criteria:** Resident of East Boston Age ≥ 65 yo Non-institutionalized. **Exclusion criteria:** NR	**Risk factor/exposure 1:** BP at baseline; SBP classified into 5 groups (130-139 referent); DBP classified into 4 groups (70-79 referent) **Method of assessing risk factor/exposure 1:** Direct measurement based on average of 3 measures 30 seconds apart **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Time in study **Method(s) of assessing cognitive**	**1) Follow-up rate:** 3657 at baseline; 2736 (75%) SPMSQ and 2679 (73%) EBMT at 3 years, 524 died in interval; 1994 (54.5%) SPMSQ and 1970 EBMT (53.9%), 631 died in interval **2) Important baseline differences:** Significant differences between BP groups on multiple factors: baseline cognition, age, education, vascular risk factors **3) Outcome of interest #1** Overall, BP at baseline or 9 years earlier was not associated with 6 year change in cognition. Only those with SBP ≥ 160 9 years prior to baseline 1 of the 5 SBP groups) had a greater increase in SPMSQ errors over time	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial, uncertain responsiveness to change 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?:

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment: 6 years 9-15 years in subsample age 65-81		**status:** 9-item SPMSQ 6-item East Boston Memory Test Stratified analyses by antihypertensive med use and medical comorbidities		Yes
Gonzalez, Bowen and Fisher, 2008 Health and Retirement Study—HRS Merged with AHEAD cohort	**Geographical location:** United States **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 18,465 **Duration of follow up:** 6 years **Time from risk factor assessment to final cognitive assessment:** 6 years	**Age:** Range: 51 to 80+ **Sex:** Female: 10,867 (57.2%) Male: 7,598 (42.8%) **Race/ethnicity:** [n (%)] White: 15,334 (87.7%) Nonwhite: 3,119 (12.3%) **Baseline cognitive status:** Nationally representative sample, irrespective of baseline cognitive status **Inclusion criteria:** Multistage probability sample, reportedly representative of the U.S. population over age 50 in 1998. **Exclusion criteria:** Institutionalized	**Risk factor/exposure 1:** Depressive symptoms **Method of assessing risk factor/exposure 1:** Self-report. Depressive Sxs in the week prior to interview. CES-D scale. 8-item version. Score range 0-8 **Risk factor/exposure 1:** Cardiovascular risk factors. **Method of assessing risk factor/exposure 1:** Self report. Respondents asked if a doctor ever told them they had diabetes, stroke, HTN, or CVD	**1) Follow-up rate:** 72.3% combined year response rate. Wave-to-wave re-interview response rates ranged from 92.1% to 87.5%. **2) Important baseline differences:** NA **3) Outcome of interest #1** Depressive sxs were associated with significantly lower Immediate (-0.05; p<0.001) and Delayed (=-0.06; p<0.001) word list recall scores. **4) Outcome of interest #2** Depressive Sx: Betas and SE: Immediate recall: -0.05 (0.00), p<0.001 Delayed recall: -0.06 (0.00), p<0.001 **5) Outcome of interest #3** CVD risk factors Betas and SE: Immediate recall: -0.07 (0.001), p<0.001 Delayed recall: -0.10 (0.00), p value not reported, but > 0.001	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Covariates/potential confounders adjusted for in analyses: Age Race Sex Educational level Wordlist exposure frequency Households with more than 1 respondent **Method(s) of assessing cognitive status:** Verbal learning and memory of a 10-word list learning task Immediate recall: immediately after having been read a list of 10 words. Delayed: after 3 minutes of interference tasks. **Informant interview?:** No		
Graves, Rajaram, Bowen, et al., 1999 KAME Project	**Geographical location:** King County, Washington, USA **Setting:** Community Clinical –	**Age:** Range: 65-95+ **Sex:** [n (%)] Female: 1028(56%) Male: 808 (44%) **Race/ethnicity:** [n (%)]	**Risk factor/exposure 1:** Migration history, education, number of years lived in Japan before age 18 y, age at which English became main language spoken	**1) Follow-up rate:** 87% completed 2 year follow up. 77 died 117 refused 2nd testing. 37 moved or where lost to f/u **2) Important baseline differences:** NR.	**Comments:** Question 2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial 2) Selection minimizes baseline

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	institutionalized and non institutionalized patients in the census **Study design:** Prospective cohort **Number of participants enrolled:** 1836 at baseline 1604 at 2 yr follow up **Duration of follow up:** 2 years **Time from risk factor assessment to final cognitive assessment:** Life-long exposure or since childhood. Measurement is 2 years follow up for cognition.	Japanese origin (96%) Japanese American (1 parent only Japanese) 4% **Baseline cognitive status:** Non-demented **Inclusion criteria:** 65 y or older Living in King County, WA With Japanese Heritage; 1 or 2 parents Japanese. **Exclusion criteria:** Dementia Younger than 65	at home, language usually spoken at home currently, current facility with reading and writing Japanese. **Method of assessing risk factor/exposure 1:** Self-report With highly structured interview **Risk factor/exposure 2:** Friends growing up being mainly Japanese vs. non Japanese, or even number of both. Current friends Japanese, non Japanese or even number of both. Current religion. Diet consistent of mainly Asian food, Asiand and western equally or mainly western. **Method of assessing risk factor/exposure 2:** Self-report with highly structured interview. **Covariates/potential confounders adjusted for in analyses:** Age Sex	**3) Outcome of interest #1** CASI mean change -1 SD of -5.15 points= 144 decliners 1455 non decliners **4) Outcome of interest #2** After adjusting for baseline age, sex, baseline CASI score, education and follow up time the results are as follows: - Home language only/mostly Japanese: OR:0.45 CI 0.23-0.86, p<.01 - English Home language after 40 y : OR 0.42, CI 0.21-0.81 p<.01 - Baseline interview taken in Japanese: OR0.38, CI 0.21-0.69 p<.01 - Generation Issei (born in Japan) OR 0.28, CI 0.13-0.58 p<.01; - Kibei (born in US, Japan education) OR 0.58, CI 0.33-1, p<.05, compared to US born and educated - Any education in Japan: OR 0.44, CI: 0.27-0.73, p<.01 - Years lived in Japan1-7 OR 0.46, CI 0.23-0.91, P<.05; - Years lived in Japan 8-15: OR0.38, CI 0.19-0.78, p<.01; - Years lived in Japan 16-18: OR 0.32, CI 0.15-0.69, p<.01, compared to 0 years - Reads/write Japanese with no difficulty: OR 0.42, CI: 0.23-0.77, p<.01; - Reads /write with difficulty OR 0.96, CI 0.62- 1.47; compared to Does not read/write Japanese	differences in prognostic factors?: Yes. 3) Sample size calculated/5% difference?: No. 4) Adequate description of the cohort?: Yes. 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Educational level Baseline cognitive status f/u time **Method(s) of assessing cognitive status:** Other – CASI (cognitive abilities screening instrument) decline was defined as mean change – 1 SD, ie:>5.15 points loss in 2 yrs. Random measurement error inherent in CASI taken into account. **Informant interview?:** No	-Current friends mostly Japanese: OR0.64, CI 0.44-0.93, p<.01; Past friends mostly Japanese OR 0.91, CI 0.63-1.33 **5) Outcome of interest #3** - Eastern religion (Buddhist, Shinto) OR 1.34, CI 0.87-2.07 - - Eat only Asian foods OR 0.96, CI 0.62-1.49.	
Gray, Anderson, Crane, et al., 2008 Adult Changes in Thought study (ACT)	**Geographical location:** Seattle, WA **Setting:** Clinical – Group Health Cooperative **Study design:** Prospective cohort **Number of participants enrolled:** 2969 **Duration of follow up:** Mean 5.5 (+ 2.7) yrs	**Age:** Mean (SD): Group A 75.4 (6.2) Group B 76.1 (6.6) Group C 75.4 (6.2) **Sex:** [n (%)] Female: 1768 (60%) Male: 1201 (40%) **Race/ethnicity:** [n (%)] Caucasian 2681(90.3%) Other 288 (9.7%) **Baseline cognitive status:**	**Risk factor/exposure 1:** Nutritional intake of Vit C, E, or multivitamins (MVI) for at least 1 week during the previous month at baseline. **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2:** APOE	**1) Follow-up rate:** 2969/3392 (87.5%) **2) Important baseline differences:** NA **3) Outcome of interest #1** Primary analysis examined whether baseline vitamin E or C use was associated with incident AD, compared with nonuse: no vitamin E, vitamin C, or MVI. Also looked at potential synergistic effect of Vitamin E and C. Results: "No difference was found in	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial 6) Validated method for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Time from risk factor assessment to final cognitive assessment: Mean 5.5 (+ 2.7) yrs	Non-demented **Inclusion criteria:** Participating in Adult Changes in Thought (ACT) study; free of dementia (CASI ≥86, or scored <86 but had no evidence of dementia based on additional medical record review and standard clinical and neuropsychological evaluation for dementia) **Exclusion criteria:** NR	**Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Exercise Smoking status Self-reported health Coronary heart disease **Method(s) of assessing cognitive status:** Screened with CASI every 2 years. If score <86, underwent dementia diagnostic eval. Relevent lab tests and brain CT performed or obtained from records. NINCDS-ADRDA DSM IV **Informant interview?:** No	degree of association between supplement use and overall dementia or AD risk when stratified according to age." **4) Outcome of interest #2—AD** Adjusted HR's (95% CI) for possible or probable AD. 1. No vitamins (n=106): 1.0 (referent) 2. Any Vit. E (n=89): 1.04 (.78-1.39) 3. Any Vit. C (n=105): 0.95 (.72-1.25) 4. Any MVI (n=134): 0.94 (.72-1.22)	ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes: 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Green, Rebok and Lyketsos, 2008	**Geographical location:** Baltimore, USA	**Age:** Mean (SD): 47.3 at enrollment.	**Risk factor/exposure 1:** Network size	**1) Follow-up rate:** 33.53% 874 out of 2607	**Comments:** Follow up rate is poor and there are significant differences between the groups that were followed and those

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
BLSA	**Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3481 adults interviewed at wave 1 1920 interviewed at wave 3 and 1071 interviewed at wave 4. 874 included in this analysis. **Duration of follow up:** 10.9 yrs. **Time from risk factor assessment to final cognitive assessment:** 10.9 yrs.	**Sex:** [n (%)] Female: 550 (62.9%) Male: 324 (37.1) **Race/ethnicity:** [n (%)] AA 322 (36.8%) White 526 (60.2%) Other 26 (2.97) **Baseline cognitive status:** Mean MMSE 28.9 but individuals with decreased cognition not specifically excluded **Inclusion criteria:** Participants having cognitive scores at wave 3 and 4 **Exclusion criteria:** NR	**Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2:** Frequency of interaction **Method of assessing risk factor/exposure 2:** Self-report **Risk factor/exposure 3:** Emotional support **Method of assessing risk factor/exposure 3:** Self report. **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Past year household income Depressive symptomatology Lifetime alcohol use disorder, Ability to perform ADLs Cerebrovascular disease.	**2) Important baseline differences:** Assessed participants were younger, had more education, higher income and higher MMSE scores. **3) Outcome of interest #1** After adjustment of covariates, participants with more frequent contacts at baseline exhibited greater decline in delayed recall p = 0.042. When this was controlled for health factors, p= 0.057**.** **4) Outcome of interest #2** After adjusting for Age Race Sex Educational level Past year household income Depressive symptomatology Lifetime alcohol use disorder, Ability to perform ADLs Cerebrovascular disease change in MMSE was not significantly affected by network size β= 0.028 (-0.037, 0.093) p= 0.403; frequency of contact β= 0.002 (-0.073, 0.078) p= 0.950; emotional support β = -0.004 (-0.047, 0.040) p= 0.862; or composite social network β = 0.005 (-0.023, 0.033) p = 0.721 at wave 3.	who were lost to follow up. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: No 2) Selection minimizes baseline differences in prognostic factors?: No 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Baseline cognitive status **Method(s) of assessing cognitive status:** MMSE Delayed recall **Informant interview?:** No		
Grodstein, Skarupski, Bienias, et al., 2008 CHAP (Chicago)	**Geographical location:** 3 neighborhoods (Morgan Park, Beverly, & Washington Heights) in south Chicago, IL **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 4409 **Duration of follow up:** From 3 to 9 years **Time from risk factor assessment to final cognitive assessment:** from 3 to 9 years Details on lifetime use of NSAIDS collected at Cycle 2 – concurrent	**Age:** Range: 65+ yo **Sex:** [n (%)] Female: 2722 (61.7%) Male: 1687 (38.3%) **Race/ethnicity:** [n (%)] White 1699 (38.5%) Black 2710 (61.5%) **Baseline cognitive status:** did not remove demented folks (or even dx dementia) **Inclusion criteria:** ≥ 65 yo; completed baseline & at least 1 f/u interview **Exclusion criteria:** NR	**Risk factor/exposure 1:** nsaids **Method of assessing risk factor/exposure 1:** checked pill bottles, self reported duration of use **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Interaction of time with each Cardiovascular factors **Method(s) of assessing cognitive status:** change in test scores	**1) Follow-up rate:** 90% did 3 follow ups, 80% did all four **2) Important baseline differences:** ASA users higher educ, more whites, more strokes NSAID users-more joint pain Both ASA and NSAID-higher global cognitive score **3) Outcome of interest #1** No relation of current use of ASA or NSAIDS to cog decl. **4) Outcome of interest #2** No relation to longer use of ASA. **5) Outcome of interest #3** For NSAIDS, longer use assoc. with slower cog. decl. For analysis with the lowest 10% of baseline scores out, mean cog decline of 0.009 (p=0.02) with short use; 0.013 (p-0.06) with longer use. (NSAIDS) Data not changed in this analysis with ASA.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	with one time point of cognitive change score – also new users of NSAIDS could be identified in Cycle 2		**Informant interview?:** No		

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Haag, Hofman, Koudstaal, et al., 2009a The Rotterdam Study	**Geographical location:** Rotterdam, The Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 6992 **Duration of follow up:** Mean 9.2 yrs (up to 15.3 yrs) **Time from risk factor assessment to final cognitive assessment:** Anytime prior to event	**Age:** Mean (SD): 69.4 (9.1) **Sex:** [n (%)] Female: 4195 (60%) Male: 2797 (40%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age ≥55; residing in Ommoord, NE **Exclusion criteria:** Dementia; <6 mos medication history	**Risk factor/exposure 1:** statins – Simvastatin (58.7%) Pravastatin (13.5%) Atrovastatin (13%) Fluvastatin (5.7%) Cerivastatin (0.5%) Rosuvastatin (0.2%) Non-statin cholesterol lowering drugs (8.4%) of Rx **Method of assessing risk factor/exposure 1:** Direct measurement Other – pharmacy records **Risk factor/exposure 2:** Age, sex, education level, smoking **Method of assessing risk factor/exposure 2:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age, Sex, use of other lipid lowering agents, education, systolic blood pressure, smoking, total serum	**1) Follow-up rate:** NR 438 people who were not exposed to statins developed AD. HR = 1.00 (REF) 28 people who were on statins developed dementia. HR= 0.57 (0.37-0.90)	**Comments:** Very good exposure data based on pharmacy records (but no data on adherence) **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell, not reported in this manuscript but sample comparable to other reports from this study that had adequate follow-up rates. 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			cholesterol, BMI, DM, cardiovascular illnesses and cerebrovascular illnesses. **Method(s) of assessing cognitive status:** NINCDS-ADRDA Other – MMSE<26 OR Geriatric Mental State organic level >0 underwent Cambridge examination for mental disorders of the elderly. If dementia suspected, "more extensive neuropsychological testing was performed." Incident dementia from medical records (GP and Mental Health) **Informant interview?:** No		
Haag, Hofman, Koudstaal, et al., 2009b Rotterdam study	**Geographical location:** Ommoord, a district of Rotterdam, the Netherlands **Setting:** Community **Study design:** Prospective cohort	**Age:** Mean (SD): 68.4 **Sex:** [n (%)] Female: 3749 (60%) Male: 2500 (40%) **Race/ethnicity:** [n (%)] Caucasian 6249 (100%) **Baseline cognitive**	**Risk factor/exposure 1:** antihypertensives **Method of assessing risk factor/exposure 1:** Other – pharmacy record **Covariates/potential confounders**	**1) Follow-up rate:** 6249/7046= 88.7% **2) Important baseline differences:** NR **3) Outcome of interest #1** Model II HR for AD (432 cases) Any Anti-hypertensive Never use: 1.0 <1.6 years 0.91 (.71-1.17) 1.6-5.3 years: 0.73 (.55-.96)	**Comments:** Question 1 Antihypertensive use was associated with a reduced risk of all dementia (adjusted HR per year of use 0.95; (95% CI 0.91–0.99). An 8% (-15% to -1%) risk reduction per year of use for persons ≤75 years was observed, whereas for persons >75 years this was 4% (95% CI -11% to 4%). Equivalent estimates were

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Number of participants enrolled: 6249 **Duration of follow up:** Up to 13.3 years Average 8 years **Time from risk factor assessment to final cognitive assessment:** average 8 years	**status:** Non-demented **Inclusion criteria:** All persons aged _55 years living in Ommoord, a district of Rotterdam, were invited to participate. Of 10,275 eligible persons, 7,983 (78%) signed informed consent. Of these, 7,528 (94%) were screened for dementia and 7,046 were free of dementia at baseline **Exclusion criteria:** dementia	**adjusted for in analyses:** Age Sex Educational level systolic and diastolic blood pressure, current smoking, total serum cholesterol, body mass index, diabetes mellitus, and cardiovascular and cerebrovascular disease. All analyses were adjusted for age, sex, and systolic and diastolic blood pressure (model I). To adjust for potential confounders (model II) included smoking, total serum cholesterol, education, body mass index, diabetes mellitus, and cardiovascular and cerebrovascular disease . **Method(s) of assessing cognitive status:** DSM III-R NINCDS-ADRDA **Informant interview?:** No	>5.3 years 0.69 (.46-1.05) HR per year treatment: 0.94 (.90-.99) **4) Outcome of interest #2** Antihypertensive use by age: Model II HR for AD Age <75 or >75 no significant association between use of antihypertensives and AD **5) Outcome of interest #3** Model II HR for AD No differences were found between classes of antihypertensive medications and AD.	observed for AD. No apparent differences were observed among different types of antihypertensive drugs. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Haan, Shemanski, Jagust, et al., 1999 Cardiovascular Health Study (CHS)	**Geographical location:** Medicare files: Forsyth County,NC Sacramento County, CA; Washington County, MD; Pittsburgh, PA **Setting:** Community Other – Medicare files **Study design:** Prospective cohort **Number of participants enrolled:** Not clear- number of subjects with testing at each year is listed. 3622 subjects had 3MS at 7 year followup (listed as year 9 in Table 1); 3333 had digit symbol substitution test. **Duration of follow up:** 5-7 years **Time from risk factor assessment to final cognitive assessment:** 5 years one cohort; 7 years other cohort	**Age:** Range: ≥ 65 years **Sex:** [n (%)] Female: 57% Male: 43% **Race/ethnicity:** [n (%)] 85% white 5% black **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residence in counties of interest; Age≥65; not institutionalized; Able to give informed consent **Exclusion criteria:** Age<65; not able to give informed consent.	**Risk factor/exposure 1:** Hypertension (Systolic Bp>158mm Hg) **Method of assessing risk factor/exposure 1:** Direct measurement **Risk factor/exposure 2:** Diabetes- presence also identified at biannual follow-up visit. All diabetes included in analysis. **Method of assessing risk factor/exposure 2:** Self-report and confirmed by medical record review or physician questionnaire. **Risk Factor/exposure 3:** APOE ε4 **Method of assessing risk factor/exposure 3:** Genotyping **Covariates/potential confounders adjusted for in analyses:** Age	**1) Follow-up rate:** NR **2) Important baseline differences:** NR **3) Outcome of interest #1** 7 year change Risk: Systolic BP>158 DSS- Risk absent: -.09 Risk present: -.62 P<.0001 3MSE Risk absent: -.16 Risk present: -1.12 Increase in bp of 1 sd over mean (21.84 mmHg) was associated with a decrease of 0.96 pts in 3MS over 7 years and 0.53 points in DSS over 7 years. Legend seems to indicate both were significant at p<0.0001. **4) Outcome of interest #2** 7 year change Risk Diabetes mellitus DSS- Risk absent: -.23 Risk present: -1.61 P<.0001 3MSE Risk absent: -.10 Risk present: -.71 **5) Outcome of interest #3** 7 year change Risk APOE ε4 any DSS	**Comments:** Data reported as change over 7 years of follow-up, but second cohort recruited at year 5- so they did not include this cohort in analysis- The first cohort was 95% white. Diabetes assessed at biannual f/u visits and lumped into analysis. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Race Sex Educational level Incident stroke **Method(s) of assessing cognitive status:** 3MSE Digit symbol substitution test **Informant interview?:** No	Risk absent: -.29 Risk present: -2.00 P<.0001 3MSE Risk Absent: -.42 Risk Present: -2.94 **6) Outcome of interest #4** Annual rate of change on 3MSE in subjects with and without APOEε4 AND with or without Diabetes. + APOEε4 and + DM: -.39 + APOEε4 and – DM: -.70 -APOEε4 and +DM: -.46 - APOEε4 and -DM: -.23 P<.001 for interaction (f/u year x risk factor x APOEε4) Ratio of annual decline with APOEε4 + APOEε4 and + DM: 1.67 + APOEε4 and – DM: 3.01 -APOEε4 and +DM: 1.99 - APOEε4 and -DM: 1.00 All values adjusted for age, sex, education.	
Hakansson, Rovio, Helkala, et al., 2009 CAIDE study	**Geographical location:** Kuopio and Joensuu regions in eastern Finland **Setting:** Community **Study design:** [	**Age:** Mean (SD): 50.4 (4.9) Range:65-79 **Sex:** [n (%)] NR **Race/ethnicity:** [n (%) Caucasian	**Risk factor/exposure 1:** marital status (married/cohabiting, single, divorced, or widowed) measured at mid-life and follow-up. **Method of assessing risk factor/exposure**	**1) Follow-up rate:** 1449/2000= 72% **2) Important baseline differences:** % participated in follow-up Age, % women, education, occupation physical activity, % smokers midlife, % office workers **3) Outcome of interest #1**	**Comments:** Question 1 and 2 – yes cat Dx No cognitive screening at enrollment. MMSE done at end of study. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Prospective cohort **Number of participants enrolled:** 1449 **Duration of follow up:** Average 21 years **Time from risk factor assessment to final cognitive assessment:** Average 21 years	**Baseline cognitive status:** Non-demented **Inclusion criteria:** The participants of the CAIDE study comprised a random sample of 2000 survivors from four separate population samples, originally investigated in 1972, 1977, 1982, or 1987. Age at original enrollment 30-59. **Exclusion criteria:** NR	**1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status BMI APO E Systolic BP Region of residence Smoking Occupation Physical activity at work Depression at mid-life **Method(s) of assessing cognitive status:** If MMSE score <24 then NINCDS-ADRDA DSM-IV **Informant interview?:** No	Risk of AD (44/1216) Status at mid-life Without partner 2.06 (0.9-4.7) Widowed 2.52 (0.8-7.7) Single/divorced 1.78 (0.7-4.9) **4) Outcome of interest #2** Risk of Cognitive Impairment (131/1303) Status at mid-life Without partner 2.09 (1.3-3.4) Widowed 2.76 (1.5-5.2) Single/divorced 1.56 (0.9-2.8) **5) Outcome of interest #3** Risk of MCI (78/1250) Status at mid-life Without partner 2.14 (1.2-3.8) Widowed 3.30 (1.6-6.9) Single/divorced 1.50 (0.7-3.4) With cohabiting apolipoprotein E e4 non-carriers as reference, the odds ratio for apolipoprotein E e4 carriers who had been widowed or divorced both in mid-life and later life was OR 25.55 (5.7 - 114.5, P<0.001) OR for APOE e4 carriers who were widowed or divorced both at baseline and follow-up was considerably lower with mild cognitive impairment as outcome (OR 4.68, 1.65 to 13.3) OR for those who were widowed or divorced after mid-life for mild cognitive impairment (2.66, 1.1 to 6.2) and for Alzheimer's disease (5.0, 1.4 to 17.5) were generally lower than those widowed or divorced at mid-life.	2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Hayden, Zandi, Khachaturian, et al., 2007 Cache County Study	**Geographical location:** Cache County, UT **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3383 **Duration of follow up** At least one follow up, baseline 95-96, first f/u 98-99, second 02-03 Ranged from 3 – 8 years **Time from risk factor assessment to final cognitive assessment:** ranged from 3 to 8 years approximately	**Age:** Mean (SD): NSAID users 73.7 (6.2) Non-NSAID 74.2 (6.5) **Sex:** [n (%)] Female: 1978 (58.4%) Male: 1405 (41,6%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 yo; pts contributed multiple time points for longitudinal analysis **Exclusion criteria:** Dementia @ baseline; pt provided a 3MS score at only one time point; pt provided incomplete info on NSAID use	**Risk factor/exposure 1:** NSAID use **Method of assessing risk factor/exposure 1:** self report, probe questions, pill bottles **Covariates/potential confounders adjusted for in analyses:** Age Sex, education, apoE, dm, cva, time followed up, quadratic term for time [I would not consider these to be covariates] okay **Method(s) of assessing cognitive status:** Change on the 3MS **Informant interview?:** No	**1) Follow-up rate:** 97.3% first f/u exam 66.0% second f/u exam **2) Important baseline differences:** nsaid users more likely female, htn, high chol. sl higher 3ms scores (<half a point) **3) Outcome of interest #1** No real difference with longer term users (started pre 65 yo) who have no E4. **4) Outcome of interest #2** E4 protective with earlier start nsaids. **5) Outcome of interest #3** Later onset of use(after 65 yo), those with E4 had higher scores at baseline but same change over time. **6) Outcome of Interest #4** No E4, late start, more decline	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Can't Tell
Hebert, Scherr, Bennett, et al., 2004 CHAP	**Geographical location:** Chicago, USA **Setting:** Community	**Age:** Mean (SD): 74 (6.4) **Sex:** Female: 62% Male: 38%	**Risk factor/exposure 1:** htn/bp **Method of assessing risk factor/exposure 1:**	**1) Follow-up rate:** 64% had all three visits, 36% had two visits **2) Important baseline differences:** cognitive change and bp both treated as continuous variables	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Study design: Prospective cohort **Number of participants enrolled:** 6158 **Duration of follow up:** baseline with up to six years follow up **Time from risk factor assessment to final cognitive assessment:** meds checked at baseline, bp checked every time? Cognition checked every time	**Race/ethnicity:** African American 62% White 38% **Baseline cognitive status:** can't tell from here, but this is the Chicago biracial study and I don't believe they eliminated the cognitively impaired. Baseline mmse 26.3 (4.4) **Inclusion criteria:** Age $\geq$ 65 years Live in a particular geographically defined community **Exclusion criteria:** NR	Direct measurement two sitting blood pressures done each visit, mean used. **Risk factor/exposure 2:** antihypertensives **Method of assessing risk factor/exposure 2:** Self-report of meds taken within the last two weeks done at baseline visit. Implies that pill bottles were checked also. **Covariates/potential confounders adjusted for in analyses:** Age, Race, Sex, Educational level, either systolic or diastolic bp (whichever wasn't examined, I think) **Method(s) of assessing cognitive status:** change in summary cognitive score **Informant interview?:** No	**3) Outcome of interest #1** Outcome was predicted annual change in global outcome score over a 6 year interval for 1 mmHg increase in bp. Neither sbp nor dbp were related to cognitive change. Sbp -0.0001 (-0.0003 to 0.00001) Dbp -0.00002 (-0.00036 to 0.00032) **4) Outcome of interest #2** dbp entered as a quadratic term is said to be significant in a curvilinear fashion such that 75mmHg has a minimum decline. **5) Outcome of interest #3** "None of the indicators for medications (general antihypertensives or type of antihypertensive) substantially altered the result."	2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Hee Kang,	**Geographical**	**Age:**	**Risk factor/exposure**	**1) Follow-up rate:**	**Comments:**

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Cook, Manson, et al., 2007 Women's Health Study	**location:** 11 US locations **Setting:** Community **Study design:** RCT **Test intervention** Asa 100mg & vitamin E 600 IU on alternate days **Comparator intervention(s)** placebo **Number of participants enrolled:** 6377 **Duration of follow up:** For cognition follow-up was about 4 yrs (3 time pts) 9.6 years **Time from risk factor assessment to final cognitive assessment:** first cog assessment 5.6 yrs after randomization, then q2yrs.	Mean (SD): 71.8 -71.9 Range: 70 – 81?? **Sex:** [n (%)] Female: 6377 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] White > 6058 (> 95%) **Baseline cognitive status:** Assumed Normal **Inclusion criteria:** Participating in the Women's Health Study; age 65 or older; providing information on NSAID and potential confounders in biennial questionnaires **Exclusion criteria:** No hx of CHD, CVD, CA, or other major chronic illnesses, no current use of study medications or hx of side effects from study meds	**1:** RCT 100 mg asa **Method of assessing risk factor/exposure 1:** RCT **Covariates/potential confounders adjusted for in analyses:** Age baseline score, perceived change in memory, cigarettes, education, etoh, bmi, physical activity, hrt, dm, htn, hyperchol, depression, cardiovasc dz. **Method(s) of assessing cognitive status:** Change over time on various cognitive measures **Informant interview?:** No	79.5% all cognitive assessment, 80% all assessments, 79% placebo **2) Important baseline differences:** none **3) Outcome of interest #1** No differences were observed in mean change in cognitive performance by treatment assignment for cognitive outcome.	None **Quality assessment:** *For RCTs:* 1) Baseline comparability?: yes 2) Valid AD/cognitive outcomes assessment?: Yes 3) Subjects/providers blind?: Yes 4) Outcome assessors blind?: Yes 5) Incomplete data adequately addressed?: Yes 6) Differential dropout rate < 10%?: Yes 7) Overall dropout rate < 30%?: Yes 8) Conflict of interest reported and insignificant?: Yes 9) Randomization adequate?: Yes 10) Allocation concealment adequate?: Yes
Hee Kang and Grodstein, 2003	**Geographical location:** 11 US States	**Age:** Range: 70 – 81 yo **Sex:** [n (%)]	**Risk factor/exposure 1:** nsaids/asa	**1) Follow-up rate:** 93% did baseline. Of those 90% did follow up.	**Comments:** Findings stated more strongly by authors in the abstract

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Nurses' Health Cohort	**Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 16,128 **Duration of follow up:** exposure 1980 and q2yrs until 1998, cognition baseline and 2 years later **Time from risk factor assessment to final cognitive assessment:** f/up cog testing 2 yrs after baseline which was 1995-2001	Female: 16,128 (100%) Male: 0 (0%) **Race/ethnicity:** NR **Baseline cognitive status:** Used cohort from ongoing study, didn't give categorical dx **Inclusion criteria:** Had answered the most recent f/u questionnaire; were free of diagnosed stroke; had complete information on NSAID and aspirin use **Exclusion criteria:** diagnosed stroke; otherwise it looks like they took everyone over 70	**Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Categorical value for each test, hx dm, hx heart disease, vit E, hrt, menopause age, bmi, cigarettes, alcohol, mental health index, energy fatigue index **Method(s) of assessing cognitive status:** decline in testing scores **Informant interview?:** No	**2) Important baseline differences:** asa and nsaid users: sl less educ, poorer health, more htn, dm, cad, more use of other meds incl antidepressants, vit E, hrt nsaid users but not asa users more likely to be obese. **3) Outcome of interest #1** many analyses and done individually for each test but over all: RR of global score decline for use of nsaids 3 years before testing: 0.95 (0.70-1.29)	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial, self-report 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Helmer, Damon, Letenneur, et al., 1999 PAQUID	**Geographical location:** Southwestern France **Setting:** Community **Study design:** Prospective cohort	**Age:** Mean (SD): NR 1822 older than 74 yrs at baseline. **Sex:** Female: 2133 (58%) Male: 1541 (42%) **Race/ethnicity:**	**Risk factor/exposure 1:** Marital Status **Method of assessing risk factor/exposure 1:** Self-report 1) Married or	**1) Follow-up rate:** 3675 nondemented participants: 794 (21.6%) lost to followup (365 died, 12 lost to f/u, 417 refused f/u).b Follow-up rate: 2881/3675 = 78.4% **2) Important baseline differences:** NA	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Number of participants enrolled: 5554 in cohort, 3777 (68%) agreed to participate. **Duration of follow up:** 4.3 yrs (SD 1.4) **Time from risk factor assessment to final cognitive assessment:** 4.3 yrs (SD 1.4)	NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Living at home in Southwestern France, age 65 yrs or older, **Exclusion criteria:** NR	cohabitant (n=2106) 2) Never married (179) 3) Widowed (n=1287) 4) Divorced or separated (n=103) 215 initially married who became widowed during the f/u period were considered married until the death of their spouses, and then considered widowed. **Covariates/potential confounders adjusted for in analyses:** Number of people in the social network. Satisfaction with work, living alone, number of leisure activities. Baseline CED-D score. Education and wine consumption. Stratified for sex. Cox model with delayed entry taking age at the time scale. **Method(s) of assessing cognitive status:** Home interviews. First, patients with suspected dementia were diagnosed using DSM IIIR criteria. Then seen by a senior neurologist who	**3) Outcome of interest #1--AD** 190 incident cases of dementia, 140 of which were AD and 50 "other." **4) Outcome of interest #2—Association between marital status and AD** A) Reference: Married (n=44) B) Widowed (n=74): RR 0.82 (95%CI: 0.46-1.44), p=0.487 C) Never married (n=18): RR 2.31 (95% CI: 1.14-4.68), p0.02 D) Divorced (n=4); RR 0.93 (95% CI: 0.26-3.31), p=0.917 **5) Outcome of interest #3** Authors' conclusion: "Our results…confirm that never-married individuals have a significantly higher risk of dementia or AD than married ones—a twofold increase for the risk of AD."	3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			confirmed the diagnoses and applied NINCDS-ADRDA criteria. **Informant interview?:** No		
Ho, Niti, Yap, et al., 2008 Singapore Longitudinal Ageing Studies	**Geographical location:** South East Singapore **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1352 **Duration of follow up:** 1-2 yrs (mean 1.4 yrs – 0.5SD) **Time from risk factor assessment to final cognitive assessment:** 1-2 years with mean 1.4 years and median 1.5 years.	**Age:** Mean (SD): Group A = 64.6 (6.9) Group B = 66.2 (6.9) **Sex:** [n (%)] Female: 896 (66%) Male: 456 (34%) **Race/ethnicity:** [n (%)] Chinese **Baseline cognitive status:** Normal Defined by MMSE score ≥24 **Inclusion criteria:** Chinese older adults without cognitive impairment (MMSE <24) and without cardio-vascular disease and stroke; not mentally, physically, or functionally incapacitated **Exclusion criteria:** MMSE score<24 No stroke or	**Risk factor/exposure 1:** metabolic syndrome (international diabetic federation criteria) **Method of assessing risk factor/exposure 1:** Direct measurement **Risk factor/exposure 2:** metabolic syndrome **Method of assessing risk factor/exposure 2:** Direct measurement waist circumference >90 cm or 80cm Chinese men, women; plus any 2 of following 1. systolic bp>130, diastolic >85. 2. Elevated fasting glucose >5.6mmol/L or on diabetes drug; 3. Elevated triglycerides >1.7mmol/L or on lipid lowering drug; low HDL <0.9mmol/L in men	**1) Follow-up rate:** 2611 at baseline; 1674 reinterviewed (64%); selected 1357 cognitively unimpaired- 1352 with complete baseline and followup data **2) Important baseline differences:** Subjects lost to followup more likely men and had lower MMSE scores. Of people included- Metabolic syndrome more likely to be older, female, have less than 6 yrs education, have low leisure activities; and low baseline MMSE **3) Outcome of interest #1** MMSE 2 pt decline Metabolic Syndrome more likely to have 2 pt decline MMSE 14 vs 19.9% p<.008 (OR for Metabolic syndrome 1.42 (1.10-1.98) p<0.008)- adjusted for age, gender, education, smoking, alcohol; depression, apoe4 status, level leisure activities, baseline MMSE and length of f/u **4) Outcome of interest #2** MMSE 2 point decline- adjusted for HTN OR 1.01 (0.7-1.45)	**Comments:** Described as prospective cohort study, but population selected from individuals who have completed baseline and f/u assessment- only 64% of population completed both assessments. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial 2) Selection minimizes baseline differences in prognostic factors?: Yes. 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial 10) Analysis controls for confounding?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		cardiovascular disease	and <1.1mmol/L women or lipid lowering agent. **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level (> or <6 years) Baseline cognitive status APOE Depression Current alcohol smoking Leisure activities (physical, social or productive) **Method(s) of assessing cognitive status:** MMSE ≥24 **Informant interview?:** No		11) Analytic methods appropriate?: Yes.
Ho, Woo, Sham, et al., 2001	**Geographical location:** Hong Kong **Setting:** Community **Study design:** Prospective cohort	**Age:** Range: 70 to 90+ **Sex:** Female: 469 (47.5%) Male: 519 (52.5%) **Race/ethnicity:** NR	**Risk factor/exposure 1:** Sociodemographic and health factors **Method of assessing risk factor/exposure 1:** Self-report	**1) Follow-up rate:** 988 of the1200 (83.2%). 996 were alive at f/u. **2) Important baseline differences:** NA **3) Outcome of interest #1—Education** No formal education vs. formal	**Comments:** Few details provided about risk factor assessment. Many independent variables included in the analysis were not reported. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Number of participants enrolled: 2032 initial cohort. Of these, 1200 selected by stratified random sampling. **Duration of follow up:** 3 years **Time from risk factor assessment to final cognitive assessment:** 3 years	**Baseline cognitive status:** Non-demented No cognitive impairment **Inclusion criteria:** Elderly subjects ≥30 yrs identified by stratified (by age) disproportional random sampling among Old Age Allowance Scheme, which covers 90% of the Hong Kong elderly population. **Exclusion criteria:** Cognitive impairment or dementia at baseline	Multiple risk factors assessed, including: 1) Education (no formal education vs. formal education) 2) Exercise (no vs. yes) Minimal details provided. **Covariates/potential confounders adjusted for in analyses:** Sex only **Method(s) of assessing cognitive status:** Orientation part of CAPE as screening test. 12 CAPE questions asked. CI defined as scoring ≤ 7 points on the CAPE. **Informant interview?:** No	education: OR 3.2 (95% CI: 1.8, 5.5) **4) Outcome of interest #2—Exercise** No vs. yes: OR 2.1 (95% CI: 1.3, 3.3)	2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Can't Tell 6) Validated method for ascertaining clinical outcomes?: Yes (CAPE) 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Partial (sex only) 11) Analytic methods appropriate?: Yes
Holtzman, Rebok, Saczynski, et al., 2004 Epidemiologic	**Geographical location:** Baltimore **Setting:** Community	**Age:** Range: ≥ 50 years **Sex:** Both genders participated; statistics NR	**Risk factor/exposure 1:** Social network **Method of assessing risk factor/exposure 1:**	**1) Follow-up rate:** 40.18 % 881 eligible, 440 lost to follow up,107 had missing data. **2) Important baseline differences:** Those who were in the analysis were	**Comments:** The major threat to the validity of the article is the large amount of missing data and loss to follow up. **Quality assessment:** *For observational studies:*

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Catchment Area (ECA) Survey, Baltimore site	**Study design:** Prospective cohort **Number of participants enrolled:** 4238 enrolled in wave 1, however, only 881 met inclusion criteria for age and MMSE cut off. **Duration of follow up:** 12.4 years. **Time from risk factor assessment to final cognitive assessment:** 12.4 years	**Race/ethnicity:** White and non-white; statistics NR **Baseline cognitive status:** MMSE ≥ 28 **Inclusion criteria:** Age ≥ 50 MMSE ≥ 28 **Exclusion criteria:** None	Self-report **Risk factor/exposure 2:** Emotional support **Method of assessing risk factor/exposure 2:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline MMSE score Δ physical activity Δ dysphoria Lifetime presence of alcohol disorder CVD status at Wave 3 **Method(s) of assessing cognitive status:** MMSE **Informant interview?:** No	younger, had higher MMSE scores, had more education and more likely to be female that those who were excluded. **3) Outcome of interest #1** After controlling for **Δ** physical disability and **Δ** dysphoria, MMSE at baseline, lifetime presence of alcohol disorder and CVD status as of Wave 3, age, , gender, and race and educationsal level, there was a linear effect of the baseline network size on the change in MMSE scores. B= 0.18 SE= .06 β = .14 p <0.01 Effect size = 0.06 P= 0.006 The variance explained by network size was very small. For example, age explained 3.2 times the variance as social network. **4) Outcome of interest #2** After controlling for **Δ** physical disability and **Δ** dysphoria, MMSE at baseline, lifetime presence of alcohol disorder and CVD status as of Wave 3, age, , gender, and race there was a significant independent effect of education on the maintenance of cognitive function . B= 0.21; SE= .05 ; β =21; p<0.0005	1) Unbiased selection of the cohort?: No 2) Selection minimizes baseline differences in prognostic factors?: No 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes. 5) Validated method for ascertaining exposure?: No. 6) Validated method for ascertaining clinical outcomes?: Yes- though minor changes were made to the MMSE 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Huang, Zandi, Tucker, et	**Geographical location:** 4 US communities	**Age:** Mean (SD): est 71.8	**Risk factor/exposure 1:** fatty fish	**1) Follow-up rate:** difficult to tell –required that had both nutrition data and MRI to be in	**Comments:** Question 1

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
al., 2005 Cardiovascular Health Study (CHS)	Forsyth County, NC Washington, County, MD Sacramento, CA Pittsburgh, PA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2233 **Duration of follow up:** Est 9 yr **Time from risk factor assessment to final cognitive assessment:** 9 yr	**Sex:** [n (%)] Female: 1306 (58.5%) Male: 927 (41.5%) **Race/ethnicity:** White: 2166 (96.99%) Other: 67 (3.0%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥65 yr in 1989/90 Drawn from Medicare eligibility lists in 4 communities Had MRI as part of CHS study **Exclusion criteria:** NR	**Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level APOE Total energy BMI Study site income **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** No (informant interview only done for those who refused in-person assessment, were deceased or could not come to clinic for in-person interview)	analyses **2) Important baseline differences:** Individuals who ate more lean, fried fish were more likely to be male, less likely to be white, and more likely to be at NC site. Those who ate more fatty fish were more likely to be male and more likely to be at NC site. **3) Outcome of interest #1** Intake of fried fish not assoc with risk of AD 0.25-2 serv/wk: HR- 0.97 (0.67-1.4) ≥2 serv/wk: HR-0.95 (0.60-1.52) **4) Outcome of interest #2** Intake of tuna and other fish not assoc with risk of AD 0.25-2 serv/wk: HR- 0.85 (0.54-1.33) 2-4 serv/wk: HR-0.72(0.44-1.17) >4 serv/wk: HR – 0.69 (0.91-1.22)	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial 2) Selection minimizes baseline differences in prognostic factors?: Partial 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Can't Tell 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Hughes, Andel, Small, et al., 2009	**Geographical location:** locations throughout Sweden	**Age:** Mean (SD): Baseline: 48.33 (5.14) Follow-up: 79.81 (5.09)	**Risk factor/exposure 1:** fruit and vegetable consumption (1 question)	**1) Follow-up rate:** 3779 of 5588 survivors participated (68%). Of these 3318 of 3779 had	**Comments:** None **Quality assessment:** *For observational studies:*

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Swedish Twin Study – HARMONY study	**Setting:** Other –Twin Registry **Study design:** Prospective cohort **Number of participants enrolled:** 3779 (in models with covariate adjustment N = 3217) **Duration of follow up:** 31.47 yrs (0.91) **Time from risk factor assessment to final cognitive assessment:** 31.47 yrs (0.91)	**Sex:** [n (%)] Female: 2346 (62.08) Male: 1433 37.92) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Members of the Swedish Twin Registry born between 1886 and 1925 who completed questionnaire in 1967. Age **>** 65 years at time of cognitive evaluation for dementia **Exclusion criteria:** NR	**Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Smoking Alcohol use Exercise BMI Angina Marital status Total food intake **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** No	covariates collected. **2) Important baseline differences:** NR by exposure status **3) Outcome of interest #1** Medium or great fruit and vegetable intake in mid-life associated with reduced risk of AD (OR 0.60; 95% CI: 0.41-0.86) **4) Outcome of interest #2** Medium or great fruit and vegetable intake in mid-life associated with reduced risk of AD in women (OR=0.47; CI: 0.31-0.73) but not men. Interaction significant (OR=0.45; CI: 0.21-0.98) **5) Outcome of interest #3** Significant interaction (OR=0.44; CI: 0.21-0.95) also identified where those with angina and medium/great fruit and vegetable intake had lower risk of AD (OR=0.32; CI: 0.16-0.65). No significant association observed in those without angina.	1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: No 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Hughes, Borenstein, Schofield, et al., 2009 KAME	**Geographical location:** King County, WA **Setting:** Community **Study design:** Prospective cohort	**Age:** Mean (SD): 71.8 **Sex:** [n (%)] Female: 55.3 Male: 44.7 **Race/ethnicity:** [n (%)] 100% Japanese	**Risk factor/exposure 1:** BMI **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential**	**1) Follow-up rate:** 1478/1836 = 80.5% **2) Important baseline differences:** Female sex, alcohol, smoking, hypertension, hypercholesterolemia, diabetes mellitus **3) Outcome of interest #1** 129 incident dementia cases, 71	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Number of participants enrolled: 1478 **Duration of follow up:** Mean 7.8 years; *SD* 0.3 **Time from risk factor assessment to final cognitive assessment:** 7 to 9 years	**Baseline cognitive status:** Non-demented **Inclusion criteria:** a population-based prospective study of community- and institution-dwelling Japanese Americans 65 years and older living in King County, WA. **Exclusion criteria:** none	**confounders adjusted for in analyses:** Age Race Sex Educational level alcohol, smoking, hypertension, hypercholesterolemia, diabetes, angina pectoris, stroke, TIA, physical activity and APOE genotype. **Method(s) of assessing cognitive status:** CASI ≤86 triggers evaluation NINCDS-ADRDA DSM IV **Informant interview?:** Yes	incident AD cases, and 22 incident VaD cases Baseline BMI Model 4 (fully adjusted) HR 0.68 (0.31-1.51) 43/971 cases BMI Change Model 4 (fully adjusted) HR 0.21 (0.06-0.80) 43/971 **4) Outcome of interest #2** Higher baseline BMI was significantly associated with a reduced risk of AD (HR= 0.56, (0.33–0.97)) in the fully adjusted model. **5) Outcome of interest #3** Slower rate of decline in BMI was associated with a reduced risk of dementia (HR 0.37, 0.14–0.98), with the association stronger for those who were overweight or obese (HR 0.18, 0.05–0.58) compared to normal or underweight (HR 1.00, 0.18–5.66) at baseline.	3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Insel, Palmer, Stroup-Benham, et al., 2005 Hispanic Established Population for Epidemiolo	**Geographical location:** Texas, New Mexico, Colorado, Arizona, California **Setting:** Community **Study design:** Prospective cohort	**Normotensives (n=1138)** **Age:** Mean (SD): 73.3 (7.2) **Sex:** NR **Hypertensives (n=1721)** **Age:**	**Risk factor/exposure 1:** Blood pressure. **Method of assessing risk factor/exposure 1:** Direct measurement of SBP and DBP. Baseline HTN status	**1) Follow-up rate:** 3050 at baseline, with 2579 (84.6%) or 2859 (inconsistent reporting in the paper) with blood pressure readings at baseline and 1460 (56.6%) BP readings at 7 year f/u. **2) Important baseline differences:** NA **3) Outcome of interest #1:**	**Comments:** Outcome is slope of change in MMSE over time. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
gic Study of the Elderly	**Number of participants enrolled:** 3050 at baseline. **Duration of follow up:** 7 years **Time from risk factor assessment to final cognitive assessment:** 7 years	Mean (SD): 72.8 (6.8) **Sex:** NR **Race/ethnicity:** Mexican American population **Baseline cognitive status:** No exclusion for cognitive status reported. **Inclusion criteria:** Area probability sampling design of counties with a high proportion of Mexican Americans in 5 US states. Mexican American, ≥65 yrs **Exclusion criteria:** NR	defined as both self-reported HTN and SBP ≥ 140. SBP and MMSE data analyzed with a latent growth curve model. The beta parameter indicates the constant rate of change per unit of time. **Method of assessing risk factor/exposure:** Self report for: Education, self-reported diabetes, HTN, anti-HTN medication, physical activity, tobacco use. **Covariates/potential confounders adjusted for in analyses:** Age BMI Sex Income Educational level Baseline MMSE score Baseline CESD score Physical activity Lifestyle factors Diabetes Stroke Cardiovascular disease **Method(s) of assessing cognitive status:**	Numerous RF's (education, diabetes, stroke, depression, BMI, antihypertensives, smoking, physical activity) parameters reported, stratified by normotensive vs. HTN. Analysis: Regression analysis with latent growth curve models by baseline HTN status: unstandardized regression coefficients reported. Beta coefficients and SE reported below. *=p<.05, **=p<.01, ***=p<.001 <u>Normotensives</u> Education: .03 (.01)* Diabetes: .24 (.14) Depression: -.02 (.00)** BMI: 0 (.01) Anti-HTN 2: .18 (.41) Anti-HTN 3: .01 (.36) Anti-HTN 4: .81 (.34) Smoking: .02 (.11) Physical activity: .004 (.00)*** <u>Hypertensives</u> Education: .4 (.01)*** Diabetes: -.48 (.01)*** Depression: .01 (.00)** BMI: .03 (.01)*** Anti-HTN 2: -.38 (.19)* Anti-HTN 3: -.04 (.22) Anti-HTN 4: .46 (.30) Smoking: -.01 (.09) Physical activity: 0 (.00) **4) Outcome of interest #2—SBP** Authors' conclusion: "This investigation found that baseline SBP and MMSE did not predict the rate of	3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			MMSE assessed 4 times over 7 years. Used as screen for CI. **Informant interview?:** No	change of MMSE over 7 years for either normotensive or hypertensive participants." **5) Outcome of interest #3—DBP** "Because DBP did not vary greatly in either group, this was not modeled and was not included in the analysis."	
In't Veld, Ruitenberg, Hofman, et al., 2001 Rotterdam Study	**Geographical location:** Rotterdam, The Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 6416 **Duration of follow up:** Mean =2.2 years **Time from risk factor assessment to final cognitive assessment:** Mean = 2.2 years	**Age:** Range: ≥ 55 years at baseline **Sex:** Both genders included **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age >=55 y.o Living in Ommoord suburb of Rotterdam for >= 1 year **Exclusion criteria:** Dementia	**Risk factor/exposure 1:** Anti-hypertensive medication **Method of assessing risk factor/exposure 1:** Self-report Direct measurement-medication bottles 21.1% used 1 anti-HTN medication; 8.5% two and 1.7% three or more medications. b-blocker 14.6%; diuretics 15.3%; ACE inhibitor 5.7%; other 1.9% **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive	**1) Follow-up rate:** 5,571/6416 had f/u (87%) **2) Important baseline differences:** Anti-HTN medication users were: older and had higher BMI, and more likely to be female, smoke, have DM, PAD or h/o stroke **3) Outcome of interest #1** Incident dementia =118 (70 in untreated and 48 in treated groups); of these, AD=82 Any anti-HTN medication; HR for AD = 0.77 (95% CI 0.49-1.24) HR or all dementias = 0.67 (95% CI 0.45 – 1.00) Sensitivity analyses: 1) Excluding untreated subjects w/ SBP < 160 and DBP < 95; any anti-HTN use, HR for AD=0.99 (0.47 – 2.12); HR for total dementia 0.67 (0.35 – 1.32) 2) Gender: any anti-HTN use, HR for total dementia, men HR 0.52 (0.22-1.20); women HR 0.93 (0.59-1.46)	**Comments:** About 5% of participants lived in homes for the elderly **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial 7) Outcome assessment blind to exposure?: No 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			status DBP and SBP H/O stroke, DM or PAD BMI Tobacco use Independent vs home for the elderly **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM 2- stage exam ; secondary evaluation triggered by MMSE < 26 or Geriatric Mental State schedule >0. Of those who were not re-examined or who died, cognitive function assessed by close informants and general practitioners. **Informant interview?** Yes, for those in second stage of dementia screening, CAMDEX included informant interview. Also of those not directly reexamined (dead or not), some had informants.		
Irie, Fitzpatrick,	**Geographical location:**	**Age:** Mean (SD): 74 at first	**Risk factor/exposure 1:**	**1) Follow-up rate:** Uncertain as 5888 were recruited but	**Comments:** The authors conclude that having

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Lopez, et al., 2008 Cardiovascular Health Study (CHS)	Pittsburgh, PA, Forsyth County, NC, Washington county, MD, Sacramento county, CA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2547 **Duration of follow up:** Up to 10 years Mean 5.4 years **Time from risk factor assessment to final cognitive assessment:** Diabetes mellitus assessed annually.	examination 80.1 (exit) **Sex:** [n (%)] Female: 59% Male: 41% **Race/ethnicity:** [n (%)] 91.3% white 8.7% AA **Baseline cognitive status:** Non-demented **Inclusion criteria:** Random selection from Medicare eligibility lists in 4 counties. Non-demented on MMSE **Exclusion criteria:** Mild cognitive impairment and dementia	APOE genotype 602 with APOEε4 **Method of assessing risk factor/exposure 1:** Direct measurement **Risk factor/exposure 2:** Diabetes mellitus 320 diabetes (12.6%) **Method of assessing risk factor/exposure 2:** Direct measurement Medication use. **Covariates/potential confounders adjusted for in analyses:** Model 1: Age Race Educational level Model 2: age, race, education, HTN, total cholesterol, smoking, alcohol, BMI, depression status, ankle-brachial index, stroke. **Method(s) of assessing cognitive status:** NINCDS-ADRDA 3MSE DSS	only 2547 included in this analysis. Further details not available. **2) Important baseline differences:** Those with DM had higher systolic Bp, total cholesterol, BMI, lower ankle-brachial index **3) Outcome of interest #1** Compared to those without DM or APOEε4: Model 1 (see covariates) Incident AD DM only 1.45 (0.89-2.37) APOEε4 only 2.61 (1.93-3.54) Both 4.53 (2.47-8.30) Model 2 (see covariates) DM only 1.62 (0.98-2.67) APOEε4 only 2.50 (1.84-3.40) Both 4.99 (2.70-9.20)	both DM and APOEε4 increases risk to a greater extent than simple additive contributions. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: No 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Can't Tell. 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Informant interview?: Yes		
Irie, Masaki, Petrovitch, et al., 2008 Honolulu-Asia Aging Study (HAAS)	**Geographical location:** Oahu, Hawaii **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2350 **Duration of follow up:** Approximately 6 years **Time from risk factor assessment to final cognitive assessment:** NR	**Age:** Range: 71 - 90 **Sex:** Male: 100% **Race/ethnicity:** [n (%)] Japanese-American **Baseline cognitive status:** Non-demented **Inclusion criteria:** Born between 1900 and 1919 Living on Oahu, Hawaii Complete information on depression symptoms and APOE genotypes **Exclusion criteria:** Dementia Clinical dementia rating score of>=0.5 or Cognitive abilities sreening instrument score of <82 Died before first f/u exam or did not attend f/u examinations	**Risk factor/exposure 1:** Current depressive symptoms using 11-item CESD, (range 0-33), score >=9 **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Educational level Awareness of memory problem and cardiovascular risk factors (Smoking, DM-2, BMI, cholesterol level, ABI), **Method(s) of assessing cognitive status:** 3-stage screening beginning with CASI NINCDS-ADRDA **Informant interview?:** Yes	**1) Follow-up rate:** 1932/2350=82% **2) Important baseline differences:** More baseline stroke and low ABI in depressed or depressed and APOE-e4 positives **3) Outcome of interest #1**: CESD 11>=9; HR for AD = 2.9 (95% CI 1.4 to 5.9) CESD 11>=9; HR for mixed AD =2.8 (95% CI 1.5 to 5.1) **4) Outcome of interest #2** The interaction term for depression and APOE-e4 was significant in the models above. Neither Depression or APOE-e4, reference Only APOE-ef, HR for AD = 1.6 (0.8 to 3.1) Only CESD 11>=9, HR for AD = 2.2 (0.9 to 5.2) Both APOE and CESD 11 >=9, HR for AD 13.0 (4.3 to 39.5)	**Comments:** Do not adjust for gender **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Partial 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the cohort: Yes 5) Validated method for ascertaining exposure: Yes 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Yes 9) Completeness of follow-up: Yes 10) Analysis controls for confounding: Yes 11) Analytic methods appropriate: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Jonker, Comijs and Smit, 2003 Longitudinal Aging Study Amsterdam (LASA)	**Geographical location:** 3 regions in The Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 612 **Duration of follow up:** 3 yrs **Time from risk factor assessment to final cognitive assessment:** BL 92/93, f/up 95/96	**Age:** Mean (SD): NSAID- 72.6 (6.7) NSAID+ 73.1 (6.5) Range: 55 - 85 **Sex:** [n (%)] Female: 328 (53.6%) Male: 284 (46.4%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** community dwelling, reasonable mmse scores **Inclusion criteria:** Born in 1930 or before; participated in the second data collection cycle of LASA; completed all cognitive tests at both times **Exclusion criteria:** This paper doesn't really say. It implies that weighted (by expected mortality), random samples in three areas were pulled and didn't eliminate anyone. Institutionalized subjects are not mentioned.	**Risk factor/exposure 1:** prescripton nsaids/asa **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline mmse score, vascular disease, dm, RA **Method(s) of assessing cognitive status:** change in test score. **Informant interview?:** No	**1) Follow-up rate:** Group chosen retrospectively from those will all information available. Group using nsaids both times and group not using prescription nsaids. **2) Important baseline differences:** nsaid users had more vascular disease **3) Outcome of interest #1** information given for immed recall, delayed recall and coding tasks separately. The one that was "almost significant" showed an OR for NSAIDS for immed recall of 0.49 (0.23-1.05)	**Comments:** Only prescription nsaids counted. Mean mmse 26-27.5. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Kado, Karlalmangla, Huang, et al., 2005 MacArthur studies of successful aging.	**Geographical location:** Durham, North Carolina East Boston, Massachusetts New Haven, Connecticut **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1189 participated 499 with baseline data and 370 with longitudinal data analyzed **Duration of follow up:** 7 yrs **Time from risk factor assessment to final cognitive assessment:** 7 yrs	**Age:** Range: mean 74 yrs (SD=2.7 yrs) **Sex:** Female: 270 (54%) Male: 229 (46%) **Race/ethnicity:** NR **Baseline cognitive status:** population selected to be in the top third of physical and cognitive functioning for age group **Inclusion criteria:** 70 – 79 years old No disability on the Katz seven-item activities of daily living scale No more than one disability on eight self-report items regarding physical functioning Ability to hold a semi-tandem balance for ≥ 10 seconds Ability to stand from a seated position five times within 20 seconds Score of ≥ 6 on the 9-item Short Portable Mental Status	**Risk factor/exposure 1:** hcy stored frozen plasma – nonfasting-for ~8yrs **Method of assessing risk factor/exposure 1:** Direct measurement **Risk factor/exposure 2:** B6, B12, and folate **Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential confounders adjusted for in analyses**: in one model adjusted for age, sex, education, baseline physical fxn, smoking, in second model b 6 &12 and folate also added. **Method(s) of assessing cognitive status:** Change over time in the summary score from the following measures: Language 18 item	**1) Follow-up rate:** 370/499 with 79 dead, 29 with proxy interviews, 14 who refused and 7 did not complete testing **2) Important baseline differences:** NR **3) Outcome of interest #1** HCY: with first set of covariates risk ratio of 7 yr cognitive decline 1.44 (0.91-2.09) with addition of B6, B12, and folate as covariates, rr for 7 yr cognitive decline with hcy 1.11 (0.65-1.76) **4) Outcome of interest #2** Folate: with first set of covariates risk ratio for 7 yr cognitive decline was 1.71 (1.13–2.37) With addition of B6, B12, and HCY as covariates, risk ratio for 7 yr decline was 1.60 (1.01–2.31) **5) Outcome of interest #3** Vitamin B6: with first set of covariates risk ratio for 7 yr cognitive decline was 1.20 (0.74–1.81) With addition of B12, folate, and HCY as covariates risk ratio for 7 yr cognitive decline was 1.02 (0.59–1.62) **6) Outcome of interest #4** Vitamin B12: with first set of covariates risk ratio for 7 yr decline was 1.42 (0.91–2.06)	**Comments:** Participants were selected to be in top 1/3 of population, so applicability to general population is limited. Baseline cognitive status assessed by 9 question SPMSQ. To participate subjects had to have score ≥6, which would may not exclude mild dementia. Exposure measured on non-fasting samples that may not accurately reflect bioavailability of homocysteine **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		Questionnaire Ability to remember at least three of six elements on a delayed recall of a short story **Exclusion criteria:** NR	Boston Naming test Abstraction: 4 items from the Similarities subtest of the Wechsler's Adult intelligence scale Spatial ability: Copying image Incidental recall of confrontation naming Delayed recall of a story **Informant interview?:** No	With addition of B6, folate and HCY as covariates risk ratio for 7 yr decline was 1.27 (0.82–1.92)	11) Analytic methods appropriate?: Yes
Kalmijn, Feskens, Launer, et al., 1997a Zutphen Elderly Study	**Geographical location:** Zutphen, Netherlands **Setting:** Community **Study design:** Cohort **Number of participants enrolled:** 718 **Duration of follow up:** 3 years **Time from risk factor assessment to final cognitive assessment:** 3 years	**Age:** Mean (SD): 74.6 (4.2) years **Sex:** [n (%)] Female: 0 (0%) Male: 718 (100%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Can't tell **Inclusion criteria:** Male Living in Zutphen **Exclusion criteria:** NR	**Risk factor/exposure 1:** Education **Method of assessing risk factor/exposure 1:** self report Years of formal education: 1) ≤6 yrs 2) >6 yrs (reference) **Risk factor/exposure 2:** ApoE **Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential**	**1) Follow-up rate:** 560/718 (78%) in 1990, than 390/533) in 1993. Complete information in 356 **2) Important baseline differences:** NA **3) Outcome of interest #1** Association between education and cognitive decline in total group, and ApoE carriers vs. noncarriers. **4) Outcome of interest #2--Education** Total population: ≤6 yrs: OR 2.1 (95% CI: 0.9, 4.9) **5) Outcome of interest #3—** Education and ApoE interaction ApoE non carrier (n=272) ≤6 yrs: OR 3.1 (95% CI: 1.1, 8.8) ApoE carrier (n-84)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Partial, education arbitrarily dichotomized 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			confounders adjusted for in analyses: Age h/o cardiovascular disease **Method(s) of assessing cognitive status:** MMSE in 1990 and 1990. Cognitive decline defined as a drop of 2 or more points. **Informant interview?:** No	≤6 yrs: OR 0.9 (95% CI: 0.2, 3.8)	9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Kalmijn, Feskens, Launer, et al., 1997b Zutphen Elderly Study	**Geographical location:** Zutphen, Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 342 **Duration of follow up:** 3 yr **Time from risk factor assessment to final cognitive assessment:**	**Age:** NR **Sex:** [n (%)] Female: 0 (0%) Male: 342 (100%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented – most were probably non-demented – but some may have been demented **Inclusion criteria:** Born between 1900 and 1920	**Risk factor/exposure 1:** antioxidant and polyunsaturated fats **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Educational level Smoking ETOH use Energy intake Baseline cognitive status	**1) Follow-up rate:** 342/476 (but don't know reason for attrition) **2) Important baseline differences:** NR **3) Outcome of interest #1** No association between cognitive decline and linoleic acid, n-3 fatty acids, beta carotene, vitamins C and E, flavonoids. P for trends across low, medium and high tertile for each nutrient ranged from 09 – 0.9.	**Comments:** Question 2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: No 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial 7) Outcome assessment blind to exposure?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	3- 8 yrs (nutrition data used from 1985 and 1990 time point, final cognitive outcome 1993)	Completed 1990 and 1993 MMSE **Exclusion criteria:** NR	**Method(s) of assessing cognitive status:** Other – > 2 pt decline on MMSE indicated 'cognitive decline' **Informant interview?:** No		8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partial 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Kalmijn, Launer, Lindemans, et al., 1999 Rotterdam Case control subgroup	**Geographical location:** suburban Rotterdam, The Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** Baseline enrollment: 7983 Sample size for this study: 702 **Duration of follow up:** mean 2.7 (0.5) yrs. Time from risk factor assessment to final cognitive assessment: serum collected at baseline and stored for 4+ yrs	**Age:** Range: ≥ 55 years **Sex:** [n (%)] Female: 424.08 (60.5) Male: 277.92 (39.5) **Race/ethnicity:** NR **Baseline cognitive status:** case control, kind of. Random subset of cohort who had mmse done plus a group with mmse decline of <1 point per year. **Inclusion criteria:** Residents of Rotterdam Age 55 and older **Exclusion criteria:** Non Rotterdam Residents Age 54 and younger	**Risk factor/exposure 1:** hcy **Method of assessing risk factor/exposure 1:** Direct measurement of a nonfasting serum sample, frozen for 4.1 yrs (no decline) or 4.3 yrs (cog decline grp) **Covariates/potential confounders adjusted for in analyses:** Age, Sex, Educational level, Baseline mmse **Method(s) of assessing cognitive status** NINCDS-ADRDA DSM **Informant interview?:** No	**1) Follow-up rate:** groups chosen that had data available. **2) Important baseline differences:** more alcohol use in the random sample as opposed to decliners. **3) Outcome of interest #1** for middle third of hcy (12.9-15.7) as opposed to lowest tertile OR 1.14 (0.67 – 1.93), for highest third as compared to lowest third OR 0.91 (0.52 – 1.58)	**Comments:** They had a relatively brief period of follow up and selected for the most rapid cognitive decline. They selected random groups of those meeting a definition of decline and those who didn't and ran hcy on these two groups on serum that they had stored at baseline. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: No 2) Selection minimizes baseline differences in prognostic factors?: No 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind exposure?: Yes 8) Adequate follow-up period?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
					9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Kalmijn, Launer, Ott, et al., 1997 Rotterdam study	**Geographical location:** Rotterdam, Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 5386 **Duration of follow up:** 2.1 yr (0.8) **Time from risk factor assessment to final cognitive assessment:** 2.1 yr (0.8)	**Age:** Mean (SD): 67.7 (7.8) **Sex:** [n (%)] Female: 3182 (59%) Male: 2204 (41%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 55 yr; resident of specific suburb in Rotterdam, had reliable nutritional data, not demented at baseline **Exclusion criteria:** Nursing home residents	**Risk factor/exposure 1:** Fat intake **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Total energy intake **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes	**1) Follow-up rate:** 5386 had all info – not clear f/u rate **2) Important baseline differences:** NR **3) Outcome of interest #1** Used results for all dementia because mixed dementia (AD +vascular) included in these numbers Dementia (particularly that with a vascular component) associated with highest tertile of: Total fat: RR 2.4 (1.1-5.2) Saturated fat: RR 1.9 (0.9-4.0) Cholesterol: RR 1.7 (0.9-3.2) **4) Outcome of interest #2** Fish intake > 18.5 g/day associated with decreased risk of dementia (RR=0.4; 0.2-0.9) Linoleic acid – not associated with dementia (RR=0.6; 0.3-1.2)	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Can't Tell 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Kang, Ascherio and Grodstein,	**Geographical location:** 11 US states	**Age:** Mean (SD): 74 yr (but only gives 3 quintiles – so this is an estimate)	**Risk factor/exposure 1:** Fruit and vegetable	**1) Follow-up rate:** 90% completed 2nd cognitive wave of cognitive assessment	**Comments:** Question 2 Some of the differences in decline are very small – may not be clinically

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
2005 Nurses Health Study	**Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 13,388 **Duration of follow up:** 2 yrs (cognitive) **Time from risk factor assessment to final cognitive assessment:** Up to ~19 yrs (averaged diet intake from 1984 – first cognitive data (1995-2001) –and then last cognitive interview from 1997-2003	**Sex:** Female: 13,388 (100%) Male 0 (0%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented – (assume most were non-demented, but not stated in paper) **Inclusion criteria:** Parent sample: Nurses aged 30-55 in 1976 in 11 US states Current sample: ≥70 yr No hx of CVA Responded to most recent mailed questionnaire **Exclusion criteria:** NR	**Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** age, education, high blood pressure, high cholesterol, diabetes, coronary heart disease, hormone therapy, age at menopause, body mass index, smoking, antidepressant use, nonsteroidal antiinflammatory drug use, alcohol intake, physical activity, total energy intake, mental health and vitality indices of the 36-question short-form health survey (SF-36), and vitamin supplementation **Method(s) of assessing cognitive status:** TICS, episodic memory and composite test summary score **Informant interview?:** No	**2) Important baseline differences:** Highest fruit and vegetable consumption group (compared to lower groups) were more educated, less likely to take antidepressants, better health habits, greater use of vitamins and HRT, greater physical activity, less smoking **3) Outcome of interest #1** On global cognitive score, --highest quintile of vegetable intake showed less decline than the lowest quintile (mean difference 0.04 (p trend <0.01) -- highest quintile of green leafy veg showed less decline than lowest quintile (mean diff 0.05; p trend <0.001) --Highest quintile of legumes showed less decline than lowest quintile (mean diff 0.03; p trend 0.02) Highest quintile of cruciferous veg showed less decline (mean diff 0.04; 0.003 -0.07, but no sig trend) **4) Outcome of interest #2** On episodic memory highest quintile of cruciferous veg scored better (mean diff 0.05; p trend =0.02) Highest quintile on green leafy vegetables showed less decline (0.06, p trend <0.001) **5) Outcome of interest #3** On TICS highest quintile on green leafy vegetables showed less decline (0.23, p trend 0.003	significant but is statistically significant because of the large sample **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: Can't Tell 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Kang, Cook, Manson, et al., 2008 Women's Antioxidant and Folic Acid Cardiovascular Study	**Geographical location:** throughout the US **Setting:** Community **Study design:** RCT-add on to RCT **Test intervention** Vitamin E Vitamin C Beta carotene Vitamin B (Folic acid, Vitamin B-6, Vitamin B-12) **Comparator intervention(s):** placebo **Number of participants enrolled:** 2009 **Duration of follow up:** 6 yr (cognitive) **Time from risk factor assessment to final cognitive assessment:** 6.6 y (range 6.3-6.9)	**Age:** Mean (SD): 71.3 (4.2) **Sex:** [n (%)] Female: 2009 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Normal Non-demented MCI CIND AAMI AACD **Inclusion criteria:** Female health professionals $\geq$ 40 yr with CVD or $\geq$ 3 coronary risk factors. Those who completed the run-in-phase okay and had no history of cancer, active liver disease, chronic kidney failure, or use of anticoagulants, and who were willing to fore-go use of other vitamin supplements – were accepted for randomization **Exclusion criteria:**	**Risk factor/exposure 1:** Vitamin B (folic acid, B-6, B-12) **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** None **Method(s) of assessing cognitive status:** Other – Decline on cognitive measures **Informant interview?:** No	**1) Follow-up rate:** 93% randomized completed 1st cognitive assessment, 94% completed at least one fup, 83% completed at least 3 assessments. Cumulatively, though, just over 50% of those sample completed Wave 4 (this was partially due to a logistic issue) **2) Important baseline differences:** No differences **3) Outcome of interest #1** B vitamin group did not differ from the placebo group on extent of cognitive decline on any cognitive measure	**Comments:** Question: Q5 *For RCTs:* 1) Baseline comparability?: Yes 2) Valid AD/cognitive outcomes assessment?: Yes 3) Subjects/providers blind?: Yes 4) Outcome assessors blind?: Yes 5) Incomplete data adequately addressed?: Yes 6) Differential dropout rate < 10%?: Yes 7) Overall dropout rate < 30%?: No 8) Conflict of interest reported and insignificant?: Yes 9) Randomization adequate?: Yes 10) Allocation concealment adequate?: Can't tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		NR			
Kang, Cook, Manson, et al., 2006 Women's Health Study	**Geographical location:** US locations **Setting:** Community **Study design:** RCT. 10-year study, but this is a cognitive function substudy initiated 5.6 yrs after randomization. **Test intervention** Vitamin E (600 IU every other day) ASA 100 mg every other day) **Comparator intervention(s)** placebo **Number of participants enrolled:** 6377 **Duration of follow up:** 4.0 yrs (range, 2.6-5.7) **Time from risk factor assessment to final cognitive assessment:** Time from randomization (beginning of	**Age:** Mean (SD): Vit E 66.2 (4.0) Placebo 66.3 (4.1) Range: Vit E 66.1 – 89.9 Placebo 60.4 – 87.1 **Sex:** [n (%)] Female: 6377 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** NR **Inclusion criteria:** ≥ 45 yo; no history of coronary heart disease, cerebrovascular disease, cancer (except non-melanoma skin cancer), or other major chronic illnesses; did not actively use any of the study medications or have any history of adverse effects from the medications **Exclusion criteria:** NR	**Risk factor/exposure 1:** Vitamin E supplementation, 600 IU every other day, as part of RCT. Subjects also took aspirin 100 mg every other day in a factorial design. **Method of assessing risk factor/exposure 1:** RCT intervention **Covariates/potential confounders adjusted for in analyses:** NA (RCT) **Method(s) of assessing cognitive status:** 5 tests measuring general cognition, verbal memory, and category fluency. Primary, prespecified outcome was a global composite score averaging performances across all 5 cognitive tests using z scores. **Informant interview?:**	**1) Follow-up rate:** 5073/7175 (70.7%) of those initially enrolled completed all 3 assessments. 5073/6377 (80.0%) of those who completed initial baseline evaluation. **2) Important baseline differences:** None **3) Outcome of interest #1** No between-group scores on the 5 tests at any of the 3 assessments. Also no between-group differences in mean change in cognitive performance. Mean difference in cognitive change global score at final assessment was 0.00 (−0.04 to 0.04) Compared with the placebo group, the vitamin E group did not have a lower risk of substantial cognitive decline from the first through third assessment and had a relative risk (RR) of substantial decline in global score of 0.92 (95% CI, 0.77 to 1.10). For the verbal memory score, the vitamin E group had a borderline significant 15% lower risk of substantial decline compared with the placebo group (RR, 0.85; 95% CI, 0.71 to 1.02).	**Comments:** 10-year study, but this is a cognitive function substudy initiated 5.6 yrs after randomization. **Quality assessment:** *For RCTs:* 1) Baseline comparability?: Yes 2) Valid AD/cognitive outcomes assessment?: Yes 3) Subjects/providers blind?: Yes 4) Outcome assessors blind?: Yes 5) Incomplete data adequately addressed?: Yes 6) Differential dropout rate < 10%?: Yes 7) Overall dropout rate < 30%?: Yes 8) Conflict of interest reported and insignificant?: Yes 9) Randomization adequate?: Yes 10) Allocation concealment adequate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	exposure) to initial cognitive assessment was 5.6 yrs (range: 4.4-6.8 yrs). Time from randomization to final cognitive assessment was approximately 9.6 yrs.		No		
Kang, Cook, Manson, et al., 2009 Women's antioxidant cardiovascular study (WACS)	**Geographical location:** Various US locations **Setting:** Other – female nurses with history cardiovascular disease **Study design:** RCT **Test intervention :** vitamin E 402mg Beta carotene 50mg Vitamin C 500mg **Comparator intervention(s):** Matching placebo **Number of participants enrolled:** 1586 **Duration of follow up:** 5.4 years **Time from risk factor assessment to final cognitive**	**Age:** Mean (SD): 69 at randomization **Sex:** [n (%)] Female: 1586 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] 94.0% white, 3.3% black, 0.9% Latino American, 0.7% Asian American, 1.1% other/multiple races **Baseline cognitive status:** Non-demented **Inclusion criteria:** Women, aged 40 and over, at high risk, with a history of coronary artery disease, carotid endarterectomy, peripheral artery surgery, or three or more coronary heart disease risk factors	**Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status **Method(s) of assessing cognitive status:** Other – The primary outcome was a global composite score averaging all test scores (TICS, 10 word list delayed recall, East Boston Memory immediate and delay, category fluency animals) **Informant interview?:** No	**1) Follow-up rate:** Compliance 64-68% across treatment **2) Important baseline differences:** none **3) Outcome of interest #1** The primary outcome was a global composite score averaging all scores; repeated-measures analyses were used to examine cognitive change over time. Vitamin E supplementation and beta carotene supplementation were not associated with slower rates of cognitive change (mean difference in change for vitamin E versus placebo, -0.01; -0.05 to 0.04; *P*=0.78; for beta carotene, 0.03; -0.02 to 0.07; *P*=0.28). Although vitamin C supplementation was associated with better performance at the last assessment (mean difference, 0.13; 0.06 to 0.20; *P*=0.0005), it was not associated with cognitive change over time (mean difference in change, 0.02; -0.03 to 0.07; *P*_0.39).	**Comments:** Question 2 – no cat Dx **Quality assessment:** *For RCTs:* 1) Baseline comparability?: Yes 2) Valid AD/cognitive outcomes assessment?: Yes 3) Subjects/providers blind?: Yes 4) Outcome assessors blind?: Yes 5) Incomplete data adequately addressed?: Yes 6) Differential dropout rate < 10%?: Yes 7) Overall dropout rate < 30%?: Yes 8) Conflict of interest reported and insignificant?: No, conflict statement not given. 9) Randomization adequate?: Yes 10) Allocation concealment adequate?: Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment: 8.9 years (7.8-9.6)	**Exclusion criteria:** Subjects were randomized only if they reported good compliance, willingness to continue in the trial, had no history of cancer, active liver disease, or use of coumadin, and expressed continued willingness to forego the use of beta-carotene and vitamin A, C, or E supplements.			
Kang and Grodstein, 2008 Nurses' Health study subgroup	**Geographical location:** 11 US sites **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 858 **Duration of follow up:** 4 years for cognitive decline analysis **Time from risk factor assessment to final cognitive assessment:** Mean of 10 years	**Age:** Mean (SD): 65 **Sex:** [n (%)] Female: 858 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** No reported exclusion for dementia. **Inclusion criteria:** Enrolled in Nurses' Health Study cognitive study; no history of stroke. Data from patients included in the	**Risk factor/exposure 1:** Plasma antioxidant levels **Method of assessing risk factor/exposure 1:** Direct measurement 1) Total carotenoids 2) Five individual carotenoids **Covariates/potential confounders adjusted for in analyses:** Age Elapsed time Education Clinical variables Smoking	**1) Follow-up rate:** 788/858 = (91.8%) **2) Important baseline differences:** NA **3) Outcome of interest #1—Cognitive decline** "Higher plasma levels of carotenoids or tocopherols were not associated with slower decline in cognition." See Table 5 for mean differences in rate of CD over 4 years by quartile of plasma carotenoids and tocopherols.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?:

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	between blood draw and initial cognitive interview.	cognitive function subcohort. **Exclusion criteria:** Those who did not provide blood samples; those who did not have plasma carotenoids and tocopherols measured; those who were cases of heart disease, breast cancer and colon cancers in nested-case control studies	Medications Alcohol Physical activity **Method(s) of assessing cognitive status:** Initially, TICS for screening. Then gradually added 5 other cognitive tests to initial screening. 3 main outcomes: 1) global performance on test battery; 2) verbal memory; 3) TICS **Informant interview?:** No		Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Karlamangla, Miller-Martinez, Aneshensel, et al., 2009 Assets and Health Dynamics Among the Oldest Old (AHEAD) Study	**Geographical location:** USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 6476 **Duration of follow up:** 9 years **Time from risk factor**	**Age:** Mean (SD): 77.1 **Sex:** [n (%)] Female: 3970 (61.3%) Male: 2506 (38.7%) **Race/ethnicity:** [n (%)] -Non-Hispanic white 5712 (88.2%) -Non-Hispanic black 492 (7.6%) -Mexican Hispanic 110(1.7%) -Other Hispanic 91 (1.4%) -Other 71 (1.1%)	**Risk factor/exposure 1:** Demographic information (Age, sex, marital status, race/ethnicity) **Method of assessing risk factor/exposure 1:** Self reported **Risk factor/exposure 2:** Socio Economic Status (SES) as measured by highest year of school/college completed, household	**1) Follow-up rate:** 2353/6476=36.3% at all visits; 81% had at least 1 follow-up **2) Important baseline differences:** Did not report comparisons by exposure level **3) Outcome of interest #1** Mean decline with aging in total cognition score (range,0-35, SD, 6.00)= =4.1(0.68 SD) per decade(95%CI,3.8,4.4) Older cohorts, women, widows/widowers, and those never married declined faster and non-Hispanic blacks and those in the	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?:

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment to final cognitive assessment: 9 years	**Baseline cognitive status:** Non-demented (some possibly demented) **Inclusion criteria:** Participants in the AHEAD study born before 1924 **Exclusion criteria:** -Institutionalized persons -Proxy cognition testing - Missing more than one cognition subscale	wealth, and annual household income. **Method of assessing risk factor/exposure 2:** Self-reported **Covariates/potential confounders adjusted for in analyses:** -Baseline low performance -Length of participation -Imputed scores Age Gender Ethnicity Marital status, Change in marital status Survivorship **Method(s) of assessing cognitive status:** -an abbreviated version of the Telephone Interview for Cognitive Status for participants aged 79 years or younger and in-person interviews for participants older than 79 years **Informant interview?:** No	bottom income quartile declined slower. **4) Outcome of interest #2** Mean decline in total cognition score with race, income and educational level (SES, socioeconomic status) Large SES differences in baseline scores did not translate to differences in rates of cognitive decline	Yes 7) Outcome assessment blind to exposure?: Can't tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: No 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Khachaturian, Zandi, Lyketsos, et al., 2006 Cache Co.	**Geographical location:** Cache County, Utah **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 5092 at baseline; 3297 participating in this substudy **Duration of follow up:** 3 yrs **Time from risk factor assessment to final cognitive assessment:** pill bottle checked and cog eval both waves	**Age:** Range: ≥ 65 years **Sex:** Female: 59% Male: 41% **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participating in the Cache County Study **Exclusion criteria:** NR	**Risk factor/exposure 1:** antihypertensives **Method of assessing risk factor/exposure 1:** inspection of pill bottles for "current" use. **Covariates/potential confounders adjusted for in analyses:** Age, Race, Sex, number of apo E4s, hx of cva, hyperlpidemia, dm, mi, Educational level **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** not for everybody but IQCODE if unable to participate in screening and DQ if 3ms positive	**1) Follow-up rate:** 5092 baseline, 355 demented, 627 died, 802 refused to complete study, **2) Important baseline differences:** antihtn users older, less educ, fewer women, more strokes, more hyperlipidemia, more dm. more mi, more apoE4 than non antihypertensives **3) Outcome of interest #1** antihypertensive use and incident AD HR 0.64 (0.41-0.98)	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Kivipelto, Ngandu, Fratiglioni, et al., 2005 **AND**	**Geographical location:** Kuopio & Joensuu, Finland **Setting:** Community	**Age:** Mean (SD): Baseline: 50.6 (6.0) Follow-up: 71.6 (4.1) **Sex:** [n (%)] Female: 900 (62%) Male: 549 (38%)	**Risk factor/exposure 1:** htn, BMI **Method of assessing risk factor/exposure 1:**	**1) Follow-up rate:** 1449/2000 invited participated (72.5%); f/u rate from original cohort cannot be determined **2) Important baseline differences:**	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Kivipelto, Helkala, Laakso, et al., 2001 CAIDE & North Karelia Project	**Study design:** Prospective cohort **Number of participants enrolled:** 1449 **Duration of follow up:** 21 yrs (4.9) from baseline interview until cog assessment **Time from risk factor assessment to final cognitive assessment:** 21 yrs, range 11-26 yrs	**Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** unclear, but baseline measures were done in mid life when cog impairment would be unlikely **Inclusion criteria:** Survivors of 4 separate samples of the North Karelia Project and FINMONICA study; lived in two geographically defined areas; permission for BP and blood specimens to be taken **Exclusion criteria:** NR	Direct measurement Normal sbp < 140, borderline 140-159, high >159, normal dbp < 90, borderline 91-94. High > 94 Direct measurement; BMI calculated based on weight/height; Categorized as >30; 25-30 and <25 **Risk factor/exposure 2:** cholesterol; high = >=6.5 mmol/l **Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age, sex, education, and follow-up interval, Some analysis adjusted for APOE, hx MI, hx DM, hx stroke, midlife SBP and DBP, cholesterol, smoking, and ETOH use **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM	At baseline, higher BMI associated with increased age, shorter follow-up interval, higher SBP and DBP,and lower education **3) Outcome of interest #1.** Risk of AD 57 incident dementia (48 AD) Midlife borderline sbp OR 2.1 (0.8-5.0), high sbp 2.8 (1.1 – 7.2) **4) Outcome of interest #2** Midlife borderline dbp 1.4 (0.6 – 3.5) high dbp 1.7 (0.8 – 3.6) **5) Outcome of interest #3** midlife cholesterol $\geq$ 6.5 mml/l OR 2.2 (1.0- 4.7) Both high BP (>159) and high cholesterol (>=6.5 mml/l) compared to one risk factor; OR=3.5 (1.6 to 7.9) **6) Outcome of interest #4**: Obesity and incidence of AD BMI > 30: OR adjusted for covariates listed + APOE = 1.88 (95% CI 0.76 to 4.63) BMI 25-30 not associated with incident AD, OR=0.99 (0.47 to 2.15) **7) Outcome of Interest #5**: Number of midlifed vascular risk factors (BMI>30, BP >140, T Chol >252) adjusted for age, sex, education and follow-up time: OR for 1 risk factor = 1.37 (0.44 to 4.27); 2 risk factors OR=3.03 (1.03 to 8.89); 3 risk factors OR=6.21 (1.94 to 19.92)	2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Partial 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Informant interview?: No		
Knopman, Boland, Mosley, et al., 2001 ARIC	**Geographical location:** Forsyth County, NC Jackson, MS Suburban Minneapolis, MN Washington County, MD **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 10,963 **Duration of follow up:** mean 6 years (0.3). **Time from risk factor assessment to final cognitive assessment:** 6 years	**Age:** Range: 47-70 **Sex:** NR **Race/ethnicity:** 8729 white (79.6%) 2234 black (20.4%) **Baseline cognitive status:** Population formed 45-64 years of age, no cog requirements. **Inclusion criteria:** Enrolled in ARIC Study **Exclusion criteria:** History of stroke or TIA	**Risk factor/exposure 1:** nsaids **Method of assessing risk factor/exposure 1:** self report, pill bottles **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Site, cns-relevant meds (antipsychotics, antidepressants, anxioulytics, opiates, anticonvulsants, antineoplastic agents). **Method(s) of assessing cognitive status:** Change in individual thests **Informant interview?:** no	**1) Follow-up rate:** 76% at six years **2) Important baseline differences:** not well recorded This paper covers multiple risk factors **3) Outcome of interest #1** nsaid use not associated with declines on any test.	**Comments:** ASA included with nsaids, Change in individual tests. Mean change in test by risk factor given. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Yes 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Knopman, Mosley,	**Geographical location:**	**Age:** Mean (SD): 59 (4.3)	**Risk factor/exposure 1:**	**1) Follow-up rate:** 15,792 at visit 1. 12,887 in visit 3; of	**Comments:** Question 2 – no cat Dx.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Catellier, et al., 2009 ARIC study subset	4 US communites: Forsyth county, NC; Jackson, MS; Minneapolis, MN; & Washington county, MD **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1130 **Duration of follow up:** Median of 14 years **Time from risk factor assessment to final cognitive assessment:** 14 years	**Sex:** [n (%)] Female: 701 (62%) Male: 429 (38%) **Race/ethnicity:** [n (%)] African/Amer: 588 (52%) Other: 542 (48%) **Baseline cognitive status:** Normal **Inclusion criteria:** Subset of the ARIC cohort who participated in two brain MRI studies between 1993-1995 and 2004-2006. **Exclusion criteria:** Prior surgery for an aneurysm in the brain; metal fragments in the eyes, brain, or spinal cord; valvular prosthesis; cardiac pacemaker; cochlear implant; spinal-cord stimulator, or other internal electrical device; pregnancy; occupations associated with exposure to metal fragments	APOE genotype **Method of assessing risk factor/exposure 1:** TaqMan assay **Risk factor/exposure 2:** Vascular risk factors at baseline **Method of assessing risk factor/exposure 2:** Diabetes: Fasting glucose >126 mg/dl or nonfasting glucose >200 dl or self-reported h/o diabetes or treatment for diabetes in previous 2 weeks. HTN: SBP >140 mm HG or DBP >90 or any use of antihypertensive medication in previous 2 weeks. Education: self report (<12 yrs), 12-16 yrs, ≥17 yrs) **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level	these, 2891 participants aged 55 and older invited for MR imaging. 1945 completed an MR, with 1920 usable scans. 1130 completed visit 4, for a rate of 1130/1920 = 59%. **2) Important baseline differences:** N/A **3) Outcome of interest #1** Difference in average baseline cognitive test scores (P value): APOE genotype DSS: 1.06 (0.03) DWR: 0.17 (0.49) WF: 0.59 (0.405) **4) Outcome of interest #2** Difference in average baseline cognitive test scores (P value): Diabetes DSS: 0.25 (0.803) DWR: -0.19 (0.173) WF: 0.60 (0.597) **5) Outcome of interest #3** Difference in average baseline cognitive test scores (P value): HTN DSS: 1.55 (0.016) DWR: 0.15 (0.089) WF: -0.123 (0.088) **6) Outcome of interest #4** Difference in average baseline cognitive test scores (P value): Education level DSS: 6.87 (<0.001) DWR: 0.33 (<0.001) WF: 7.71 (<0.001)	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Can't tell, unclear how MRI subsample selected . 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Vascular factors Time Risk factor x time interaction **Method(s) of assessing cognitive status:** Digit Symbol Substitution (DSS); Delayed Word Recall (DWR); Word Fluency (WF) **Informant interview?:** No		
Koster, Penninx, Bosma, et al., 2005 Health, Aging and Body Compositio n study (Health ABC)	**Geographical location:** Pittsburg, PA Memphis, TN **Setting:** Community **Study design** Prospective cohort **Number of participants enrolled:** 2574 enrolled subjects out of longitudinal cohort of 3075. **Duration of follow up:** 4 yrs **Time from risk factor**	**Age:** Range: 70-79 yrs old **Sex:** both included but numbers NR **Race/ethnicity:** Black and white but actual numbers NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Well-functioning: no difficulty walking one-quarter mile or going up 10 steps without resting.	**Risk factor/exposure 1:** Education Categories: <12 yrs education 12 yrs education >12 yrs education **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex	**1) Follow-up rate:** 2088 followed up yr 4(81.1%) 486 lost to follow up (18.9%) **2) Outcome of interest #1** Cognitive decline was defined as a decrease of 5 or more points on the 3MS between baseline and 4th yr follow up. Adjusted odds ratio were significantly higher in those with low education: >12 yrs education: OR 1.00 12 yrs education: OR 1.42 (1.10-1.83) <12 yrs education: OR 2.16 (1.59-2.94 All CI 95% Two models were used for OR assessment based on slightly	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment to final cognitive assessment: 4 yrs	**Exclusion criteria:** -Active treatment for cancer most recent 3 yrs -Planned move out of study area in next 3yrs -Current participation in randomized trial of lifestyle intervention	Educational level Baseline cognitive status Study site House hold income Biomedical factors **Method(s) of assessing cognitive status:** Other – Modified Mini-Mental State Examination(3MS) **Informant interview?:** No	different covariates. Results were very similar.	8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Kritz-Silverstein, von Muhlen, Laughlin, et al., 2008 DAWN Trial	**Geographical location:** San Diego, CA **Setting:** Clinical Research Facility **Study design:** RCT **Test intervention:** 50 mg oral DHEA daily **Comparator intervention(s):** placebo **Number of participants enrolled:** 225 **Duration of follow up:**	**Age:** Mean (SD): 68 yr (8) Median: Range: 55-85 yrs **Sex:** [n (%)] Female: 115 (51%) Male: 110 (49%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status** Normal **Inclusion criteria:** Aged 55-85; non-smokers; not currently using any hormone therapy **Exclusion criteria:**	**Risk factor/exposure 1:** DHEA (dehydro Epiandrosterone) **Method of assessing risk factor/exposure 1:** RCT **Risk factor/exposure 2:** RCT **Method of assessing risk factor/exposure 2:** RCT **Covariates/potential confounders adjusted for in analyses** RCT Method(s) of assessing cognitive status: Other – modified	**1) Follow-up rate:** compliance with treatment 95% treatment, 94% placebo; 23 DHEA treatment stopped adverse events; 10 placebo stopped. Followup rate for treatment group 79.5%; placebo 91.2%. Follow up rate not reported by sex. **2) Important baseline differences:** Possibly relevant- DHEA levels in treated woman higher at baseline than placebo (p<0.003); testosterone higher in treated woman than placebo (p<.01) **3) Outcome of interest #1** Outcome comparisons made using Wilcoxon tests. No differences in treatment and placebo groups in any cognitive measure in either sex. Modified MMSE- no difference dhea	**Comments:** None **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? No. DHEA group 79.5% placebo 91.2% 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	1 yr **Time from risk factor assessment to final cognitive assessment:** 12 mos	NR	MMSE; word list; word list recall; verbal fluency; boston naming; trails b **Informant interview?:** No	treated and placebo **4) Outcome of interest #2** Word List- no difference dhea treated and placebo **5) Outcome of interest #3, 4, 5, 6** **Word List Recall**- no difference dhea treated and placebo **Verbal Fluency**- no difference dhea treated and placebo **Boston Naming**- no difference dhea treated and placebo **Trails B-** no difference dhea treated and placebo	
Kroger, Verreault, Carmichael, et al., 2009 Candadian Study of Health and Aging	**Geographical location:** 36 Canadian provinces **Setting:** Community Other 0 institutionalized individuals **Study design:** Nested case-control **Number of participants enrolled:** For 8361 non-demented, 1219 provided blood samples, 663 analytical sample **Duration of follow up:** Median of 4.9 years (IQ range 4.5-5.2)	**Age:** Mean (SD): 80 (6.0) normals; 82.5 (6.6) dementia **Sex:** [n (%)] Female: 401 (61%) Male: 262 (39%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age ≥ 65 yo Living in community or in institutions in 1991 Provided blood sample Selected for full neuropsychiatric examination	**Risk factor/exposure 1:** Total n-3 PUFAS and erythrocyte membrane omega-3 PUFAs at baseline analyzed by quartiles, above below median and as continuous variables. **Method of assessing risk factor/exposure 1:** Direct measurement **Risk factor/exposure 2:** Blood mercury levels **Method of assessing risk factor/exposure 2:** Direct measurement	**1) Follow-up rate:** 1219 with blood samples; 450 died, 68 lost to follow-up, 31 had blood samples that were missing or could not be analyzed; 663/1219 = 54% **2) Important baseline differences:** NR by exposure category; this subsample had slightly less education than overall cohort **3) Outcome of interest #1** 149 incident cases of dementia (105 AD) HR (95% CI) for quartiles of total n-3 PUFAs and AD Quartile 1: ref Quartile 2: 1.36 (0.79-2.35) Quartile 3: 0.97 (0.55-1.71) Quartile 4: 1.12 (0.63-1.98) No association for all cause dementia	**Comments:** Question 1 This is an updated analysis of Laurin 2003; sample significantly larger;. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial, race not given 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period?

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Time from risk factor assessment to final cognitive assessment: Median 4.9 years; max 10 years	**Exclusion criteria:** Dementia No viable blood sample Did not complete ≥ 1 follow-up	**Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level APOE e4, BMI, ever smoking, ETOH, diabetes mellitus, HTN, CVD, h/o stroke or MI, depression, family h/o dementia **Method(s) of assessing cognitive status:** 2-stage screening with neuropsychological evaluation for those with abnormal 3MS and random sample of normals. NINCDS-ADRDA: AD DSM-Dementia **Informant interview?:** Yes	**4) Outcome of interest #2** HR (95% CI) for quartiles of docosahexanoic acid and AD Quartile 1: ref Quartile 2: 0.81 (0.47-1.38) Quartile 3: 0.77 (0.44-1.35) Quartile 4: 0.81 (0.47-1.40) No association for all cause dementia **5) Outcome of interest #3** HR (95% CI) for quartiles of eicosapentaenoic acid and AD Quartile 1: ref Quartile 2: 1.16 (0.68-1.98) Quartile 3: 0.98 (0.56-1.71) Quartile 4: 0.89 (0.49-1.59) No association for all cause dementia **5) Outcome of interest #4** HR (95% CI) for quartiles of blood mercury and AD Quartile 1: ref Quartile 2: 0.76 (0.46-1.26) Quartile 3: 0.41 (0.23-0.74) Quartile 4: 0.56 (0.32-0.99) Higher mercury concentration also associated with lower risk for all cause dementia	Partial, time lag for mercury effects uncertain 9) Completeness of follow-up? Partial 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Kuo, Jones, Milberg, et al., 2005	**Geographical location:** Six field sites in US **Setting:**	**Age:** Mean (SD): 73.6+/-5.9 Range: 65-94 yrs old **Sex**	**Risk factor/exposure 1:** Blood pressure **Method of assessing**	**1) Follow-up rate:** NR **2) Important baseline differences:** NA	**Comments:** Patients with more severe dm or htn excluded Participant in RCT of cognitive

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Advanced Cognitive Training For Independent and Vital Elderly(ACTIVE)	Community **Study design:** Observational analysis (cohort) from a RCT **Comparator intervention(s)** All participants were randomized into three cognitive intervention groups (memory training, reasoning training or speed or processing training) and a no-contact control group. **Number of participants enrolled:** 2802 **Duration of follow up:** Annually for 2 yrs **Time from risk factor assessment to final cognitive assessment:** 2 yrs	Female: 2126(75.9%) Male: 676(24.1%) **Race/ethnicity:** White: 2017(72.0%) African American: 724 (25.8%) Hispanic: 15(0.5%) Other: 46(1.7%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** 65 yrs and older, non-demented **Exclusion criteria:** <65yrs,< 23 on MMSE, known diagnosis of AD, functionally impaired, medically unstable, recent or current participation in other cognitive training, visual, hearing or communicative impairment	**risk factor/exposure 1:** Direct measurement: obtained from a trained research assistant **Risk factor/exposure 2:** Diabetes Mellitus: **Method of assessing risk factor/exposure 2:** Self-report: obtained by asking direct question to subjects **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status Study site Intervention group Cardiovascular risk factors Tobacco use BMI **Method(s) of assessing cognitive status:** Other – MMSE: measured global cognitive function; Reasoning domain	**3) Outcome of interest #1—10 mm increase in SBP** Beta coefficient (SE), p value MMSE: -0.021 (0.016), p=.19 Memory composite: -0.020 (0.019), p=.30 Reasoning composite: -0.049 (0.019), p=.008 Speed of processing Digit Symbol Substitution test: -0.020 (0.082), p=.80 Useful Field of View: 3.049 (2.170), p=.16 **4) Outcome of interest #2--Diabetes** Beta coefficient (SE), p value MMSE: -.0.305 (0.108), p=.005 Memory composite: -.303 (0.130), p=.02 Reasoning composite: -0.108 (0.126), p=.39 Speed of processing Digit Symbol Substitution test -2.371 (0.559), p<.001 Useful Field of View: 60.936 (14.647), p<.001	training **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial: DM based on unvalidated self-report 6) Validated method for ascertaining clinical outcomes? Partial: the useful field of vision test is not well validated test for this outcome. 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			used word series, letter series and letter sets. A higher reasoning composite score indicates better performance. Speed of processing assessed using Useful Field of View(UFOV) **Informant interview?:** No		

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Laitinen, Ngandu, Rovio, et al., 2006 CAIDE Study	**Geographical location:** North Karelia and Kuopio provinces, Finland **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2000, but 1,449 participated in follow-up. Included all in analyses **Duration of follow up:** 21 (4.9) yrs (for the 1,449) **Time from risk factor assessment to final cognitive assessment:** 21(4.9) yrs	**Age:** (for 1,449) Mean (SD): midlife exam: 50.4 (6.0) yr fup exam: 71.3 (4.0) **Sex:** [n (%)] Female: 900 (62.1%) Male: 549 (37.9%) **Race:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participated in one of two other population-based studies. Alive, e, aged 65 to 79 at the end of 1997 and living in one of two geographically defined areas in or close to the towns of Kuopio and Joensuu in Finland. **Exclusion criteria:** NR	**Risk factor/exposure 1:** Fat intake **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age (midlife) Sex Educational level FUP time Milk fat and other types of fats from spreads Midlife vascular risk factors APOE History of vascular disorders collected at f/u **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM Other: ~551 non-participants at FUP, dx from medical records, assume still tried to apply above criteria **Informant interview?:** No (neither this article	**1) Follow-up rate:** not relevant because the included non-participants in analyses – 2000 selected from baseline study to be followed ~21 yr later **2) Important baseline differences:** At baseline, individuals who became demented older, less educated, had higher BMI, higher, SBP, higher cholesterol than non-demented **3) Outcome of interest #1** Total fat: 2nd, 3rd and 4th quartiles of total fat intake was not associated with increased risk of AD (compared to 1st quartile) PUFA: 3rd quartile of PUFA associated with lower risk of AD (OR-0.36; 0.16-0.82) MUFA: 2nd, 3rd and 4th quartiles of MUFA was not associated with increased risk of AD (compared to 1st quartile) SFA: 2nd quartile of SFA was not associated with increased risk of AD(compared to 1st quartile)	**Comments:** Question: Q1 Results section states that the results were very similar when analyses were limited to those who participated in the follow-up. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial. More details on non-participants at f/u needed. 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? No 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Partial. Used all subjects, even non-participants at f/u. 10) Analysis controls for confounding? Partial. Not sure how late life medical conditions were determined for the non-participants. 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			nor the methods paper mentions an informant interview)		
Larson, Wang, Bowen, et al., 2006 ACTS (Adult Changes in Thought Study)	**Geographical location:** Seattle, WA **Setting:** Clinical—Group Health Cooperative HMO **Study design:** Prospective cohort **Number of participants enrolled:** 5422 eligible, 2581 participated (2841 declined) in ACT study. 1740 in final sample, from 1895 persons in the ACT study whose CASI scores were above the 25th percentile. 155 withdrew after the baseline visit. **Duration of follow up:** 6.2 yrs (SD, 2.0) **Time from risk factor assessment to final cognitive assessment:** 6.2 yrs (SD, 2.0)	**Age:** Mean (SD): Free of dementia: 73.2 (5.1). With dementia: 78.2 (5.5) **Sex:** Female: Free of dementia: 731 (61.9%) With dementia: 93 (58.9%) Male: Free of dementia: 454 (38.1%) With dementia: 65 (41.1%) **Race/ethnicity:** Free of dementia: White: 1109 (93.7%) Black: 20 (1.7%) Other: 55 (4.6%) **Baseline cognitive status:** Normal Non-demented **Inclusion criteria:** Age ≥ 65 when study began in 1994-1996. Member of Group Health Coop HMO.	**Risk factor/exposure 1:** Physical exercise. **Method of assessing risk factor/exposure 1:** Self-report: # of days per week they did each of list of activities for at least 15 minutes at a time during the past year. Scale dichotomized "exercised regularly" defined as self-report of exercise ≥3 times/wk, vs. "did not exercise regularly." **Covariates/potential confounders adjusted for in analyses:** Age Ethnicity Sex Educational level Baseline cognitive function Physical function Depression Health conditions Lifestyle characteristics Supplements	**1) Follow-up rate:** 1740/1895 (92%). 155 withdrew after baseline visit. Random sample of 6782 members of GHC Excluded: dementia, nursing home, or participating in other studies (1360). Of 5422 eligible, 2581 participated and 2841 declined (no difference in age, sex, or ethnicity, but older, women, and minority more likely to decline). Excluded lowest quartile of CASI scores (n=686). **2) Important baseline differences:** NA **3) Outcome of interest #1** 158 incident cases of dementia (107 of which were AD and 33 were vascular dementia and 18 were other). Incidence rate 13.0/1000 person-yrs for dementia. **4) Outcome of interest #2--Dementia** Incidence rate 13.0/1000 person-yrs for persons who exercised ≥3 times/wk vs. 19.7/1000 person-yrs for persons who exercised <3 times/wk. Age- and sex-adjusted HR was 0.62	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		Participants in ACT study with CASI scores above the 25th percentile. **Exclusion criteria:** Existing diagnosis of dementia current residents of a nursing home participation in other studies.	APOE **Method(s) of assessing cognitive status:** Screened with CASI. Screen positives (CASI < 86) had additional medical record review and standardized clinical and neuropsych eval. "Cognitively intact" if CASI ≥86. NINCDS-ADRDA DSM-IV **Informant interview?:** No	(95% CI, 0.44-0.86, p=0.004). HR was 0.68 (95% CI, 0.48-0.96) when adjusted for all potential confounders. Kaplan-Meier survival estimates show that exercising ≥3 times/wk is associated with higher probability of being dementia-free. Significant interaction between exercise and performance-based physical function (p=0.013). Risk reduction associated with exercise was greater in those with lower performance levels. **5) Outcome of interest #3--AD** Age- and sex-adjusted HR was 0.64 (95% CI, 0.43-0.96, p=0.031). HR was 0.69 (95% CI, 0.45-1.05; p=0.081) when adjusted for all potential confounders. The interaction of exercise with performance-based physical function was significant (p=0.021).	
Launer, Ross, Petrovich, et al., 2000 Honolulu Heart Program	**Geographical location:** Honolulu, HI **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 8006 in initial cohort;	**Age:** Mean (SD): 52.7 (4.7) at baseline exam; 77.9 (4.7) at outcome assessment Range: 71 – 93 yo **Sex:** [n (%)] Female: 0% Male: 100% **Race/ethnicity:** [n (%)] Japanese-American	**Risk factor/exposure 1:** Measured each visit 3 times five min apart, dbp "recorded as the fifth phase" Low sbp <110, normal 110-139, borderline 140-159, high 160+, dpb low <80, nl 80-89, borderline 90-94, high 95+	**1) Follow-up rate:** 80j% of survivors participated in evaluation; non-participants had lower education and moe missing data for one of the mid-life exams **2) Important baseline differences:** high midlife sbp ore associated with with more stroke, dementia (not ad), and vascular dementia. High midlife dbp associated with more stroke. Men with low and nl baseline	**Comments:** Question 1 Dementia eval for those who were over 85 plus those who scored <74 on the casi, considerably lower than the threshold for act. No evaluation for dementia in earlier phases of study. **Quality assessment:** *For observational studies:*

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	3703 in this analysis **Duration of follow up:** >=23 years **Time from risk factor assessment to final cognitive assessment:** average of 27 years between first bp measurement and the dementia assessment	(100%) **Baseline cognitive status:** no elimination of cognitive impairment but mean age at baseline 52.7±4.7 **Inclusion criteria:** Participant in Honolulu Heart Program; Japanese-American males; born between 1900 – 1919; living in Oahu, HI at baseline; military service registered from WWII **Exclusion criteria:** 30 subjects with dementia due to PD, b12 defiiency, subdural hematoma, or supranuclear palsy)	A fifth category was created for those whose bp did not fall into a category above in 2/3 measurements. Self report of antihypertensives. **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age (at the fourth exam), education, apolipoprotein phenotype, smoking thru exam 3, alcohol at exam 3, cva, cad, subclinical atherosclerosis (abi based) **Method(s) of assessing cognitive status:** DSMIII-R - dementia NINCDS-ADRDA- AD **Informant interview?:** Yes – for those who got dementia eval	pressure 1.5 yrs younger than others. **3) Outcome of interest #1** Analysis stratified by h/o treatment or no treatment with anti-hypertensive medication. Dementia cases = 197; AD=118 Among untreated, high DBP (OR 4.47 (95% CI 1.53 to 13.09), borderline DBP (OR 3.49, 95% CI 1.28 – 9.52) but not mixed DBP (OR 1.33, 95% CI 0.54 to 3.26) associated with AD Among treated, no association between DBP and AD: high DBP (OR 0.14 (95% CI 0.02 to 1.17), borderline DBP (OR 0.71, 95% CI 0.17 – 3.00); mixed DBP (OR 1.35, 95% CI 0.49 to 3.69) Among untreated, no association between SBP and AD: high SBP (OR 1.22 (95% CI 0.37 to 4.04), borderline SBP (OR 1.23, 95% CI 0.63 – 2.43); mixed DBP (OR 0.25, 95% CI 0.05 to 1.14) Among treated, no association between SBP and AD: high SBP (OR 0.65 (95% CI 0.20 to 2.15), borderline SBP (OR 1.03, 95% CI 0.40 – 2.61); mixed DBP (OR 1.03, 95% CI 0.28 to 3.76) **4) Outcome of interest #2** high sbp (1965) and AD (1991-3) 0.56 (0.20-2.15) treated	1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? No 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				For dementia overall, DBP (high and borderline) associated with dementia in untreated but not treated group. For dementia overall, high SBP but not borderline or mixed associated with dementia in untreated but not treated group.	
Laurin, Masaki, Foley, et al., 2004 HAAS	**Geographical location:** Oahu, Hawaii **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2459 **Duration of follow up:** Range: 25.7-33.0 yrs **Time from risk factor assessment to final cognitive assessment:** Range: 25.7-33.0 yrs	**Age:** Mean (SD): At exam 4: Nondemented:76.3 (IQR 74.2-79.3) Demented: 78.9 (IQR 76.1-83.3) **Sex:** [n (%)] Female 0 (0%) Male: 2459 (100%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Men of Japanese ancestry born between 1900 and 1919 who resided on the island of Oahu, Hawaii in 1965 and were participants of the Honolulu Heart Program. **Exclusion criteria:**	**Risk factor/exposure 1:** beta-carotene, flavonoids, Vit E and C **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Educational level Smoking ETOH use BMI Physical activity Blood pressure Year of birth Total energy intake Cholesterol Hx of cardiovascular disease APOE Supplemental vitamins **Method(s) of**	**1) Follow-up rate:** NR in detail **2) Important baseline differences:** Individuals who became demented were older at baseline (p<0.001). No other differences **3) Outcome of interest #1** Beta-carotene – no difference in risk of AD and mixed AD/vasc associated with higher quartiles of intake Vitamin C - – no difference in risk of AD and mixed AD/vasc associated with higher quartiles of intake Vitamin E – 2nd and 4th quartiles only associated with higher risk of AD and mixed AD/vasc (but not the 3rd quartile) 2nd quartile: RR 1.92 (1.16-3.18) 4th quartile: RR 1.78 (1.06-2.98) Flavonoids- no difference in risk of AD associated with higher quartiles of intake No sig trends across quartiles noted for any of the anti-oxidants	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Partial 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		NR	**assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes	**4) Outcome of interest #2** Highest group of sum of all antioxidants intake associated with increased risk of AD and AD mixed/vasc dementia compared to lowest summed group. RR=1.82 (1.04-3.21)	
Laurin, Verreault, Lindsay, et al., 2001 Canadian Study of Health and Aging	**Geographical location:** All 10 Canadian provinces **Setting:** Community **Study design:** Prospective cohort AND Nested case-control **Number of participants enrolled:** 4615 **Duration of follow up:** 5 years **Time from risk factor assessment to final cognitive assessment:** 5 years	**Age:** Controls: Age 65-74: 59.5% Age 75-84: 36.6% Age >85: 3.9% Dementia: Age 65-74: 18.6% Age 75-84: 53.7% Age >85: 27.7% **Sex:** Female: Controls: 2351 (60.4%) Dementia: 175 (61.8%) Male: Controls: 1543 (39.6%) Dementia: 109 (38.2%) **Race/ethnicity:** NR **Baseline cognitive status:**	**Risk factor/exposure 1:** Physical activity **Method of assessing risk factor/exposure 1:** Self-report Combined 2 questions from the risk factor questionnaire regarding frequency and intensity of exercise for subjects who reported physical activity. Composite physical activity score categorized: 1) "low" = less than weekly 2) "moderate" = weekly 3) "high"= >3 times/wk Reference category was no physical activity (subjects who reported no physical activity) **Covariates/potential**	**1) Follow-up rate:** 4615 of 6434 initially eligible (72%). 442 excluded from the initial 9008 sample because they lived in Newfoundland, 826 had CIND or dementia. Others excluded for death, refusal, lost to follow up. **2) Important baseline differences:** NA **3) Outcome of interest #1** 285 incident cases of dementia, 436 incident cases of cognitive impairment, and 194 incident cases of AD. **4) Outcome of interest #2** High levels of physical activity were associated with reduced risks of cognitive impairment (age-, sex-, and education-adjusted OR, 0.58; 95% CI, 0.41-0.83), AD (OR, 0.50; 95% CI, 0.28-0.90), and dementia of any type (OR, 0.63; 95% CI, 0.40-0.98). **5) Outcome of interest #3** Authors' comments: "study showed a significant protective effect of regular physical	[**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		Normal Non-demented **Inclusion criteria:** 65 years or older and living in the community in one of 36 selected urban and surrounding rural areas in Canada. **Exclusion criteria:** Residents of Newfoundland, Dx of CIND or dementia at the first evaluation.	**confounders adjusted for in analyses:** Age Sex Educational level Family h/o dementia Tobacco use Alcohol use NSAID use Daily living activities Clinical variables **Method(s) of assessing cognitive status:** Screened with MMSE (screen + if MMSE ≤77). NINCDS-ADRDA DSM-IIIR (baseline) DSM-IV (follow up) **Informant interview?:** No	activity on the risk of CI and dementia, particularly of the AD type" "these associations were mainly in women, with a significant dose-response relationship with decreasing risk with increasing physical activity."	
Lautenschlager, Cox, Flicker, et al., 2008 FABS Fitness for the Aging Brain Study.	**Geographical location:** Perth Australia. **Setting:** Other – Multiple sources. **Study design:** RCT **Test intervention:** Physical activity (encouragement to	**Age:** Mean (SD): 68.6 (8.7) for the exercise group and 68.7 (8.5) for the control group **Sex:** [n (%)] Female: 42 (49.4) in the exercise groups 44 (51.8) in the control group. Male: 0 (0%)	**Risk factor/exposure 1:** Physical activity **Method of assessing risk factor/exposure 1:** Self-report Direct measurement **Risk factor/exposure 2:** Apoe	**1) Follow-up rate:** 138/170 (81.17%) **2) Important baseline differences:** None **3) Outcome of interest #1** The effect of the intervention on the entire sample (n=170)- P value for repeated measures ANOVA: Mean change of ADAS-COG scores: Between participants: 0.04 Within participants :0.54	**Comments:** Good quality RCT with methodology explicitly explained in the manuscript. **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? No 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%?

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	participate in 150 minutes of moderate intensity activity per week) with behavioral intervention to increase adherence. **Comparator intervention(s):** Usual care. **Number of participants enrolled:** 311 screened, 170 randomized (141 excluded) **Duration of follow up:** 18 months. **Time from risk factor assessment to final cognitive assessment:** 18 months.	**Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented MCI **Inclusion criteria:** Age >50 yrs Answers yes to the following question: "Do you have any difficulty with your memory?" **Exclusion criteria: .** 1)Scores lower than 19 of 50 on the Telephone Interview for Cognitive Status–Modified 2)Geriatric Depression Scale-15 score of 6 or higher 3)Drinking more than 4 standard units of alcohol a day 4)chronic mental illness, such as schizophrenia; 5) medical conditions likely to compromise survival, such as metastatic cancer, or render them unable to engage in physical activity, such as severe cardiac failure. 6) severe sensory impairment or lack of fluency in written or	**Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status (premorbid IQ) Marital Status Adjusted baseline measures of outcome **Method(s) of assessing cognitive status:** ICD CERAD MMSE **Informant interview?:** No	Word List Delayed recall: Between participants: 0.02 Within participants :0.10 No statistically significant difference for the other cognitive, health and quality of life measures. **4) Outcome of interest #2** The effect of the intervention and time on the MCI sample (n=100)- P value for repeated measures ANOVA: Mean change of ADAS-COG scores: Between participants: 0.02 Within participants :0.45 Word List Delayed recall: Between participants: 0.48 Within participants :0.55 No statistically significant difference for the other cognitive, health and quality of life measures. **5) Outcome of interest #3** The effect of the intervention and time on the complete- case analysis sample (n=138)- P value for repeated measures ANOVA: Mean change of ADAS-COG scores: Between participants: 0.0009 Within participants :0.25 Word List Delayed recall: Between participants: 0.01 Within participants :0.45	Yes 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		spoken English		CDR sum of Boxes: Between participants: 0.003 Within participants :0.64 No statistically significant difference for the other cognitive, health and quality of life measures.	
Lee, Buring, Cook, et al., 2006 Women's Health Study (WHS)	**Geographical location:** NR **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 7118 **Duration of follow up:** 2 yrs **Time from risk factor assessment to final cognitive assessment:** 2 yrs	**Age:** Range: ≥ 66 years **Sex:** Female: 100% **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Women's Health Study participants 66 yrs or older in 1998. **Exclusion criteria:** Stroke (n=69)	**Risk factor/exposure 1:** Education **Method of assessing risk factor/exposure 1:** Self-report "What is the highest level of education you have completed?" 1) Licensed practical or vocation nurse; 2) 2-year associates degree; 3) 3-year nurse diploma program (reference category); 4) Bachelors in nursing; 5) Masters degree; 6) Doctoral degree. **Covariates/potential confounders adjusted for in analyses:** BMI, physical activity, high blood pressure,	**1) Follow-up rate:** 7118 eligible. 408 (5.7%) refused, 396 (5.9%) unreachable. Final sample at baseline: 6314 (88.7%) F/u rate: 5907/6314 (93.5%). 181 (3.1%) refused, 132 (2.3%) lost to f/u, 21 (0.4%) died. **2) Important baseline differences:** NA **3) Outcome of interest #1—cognitive impairment** Refer to Table 3 in article. **4) Outcome of interest #2—cognitive decline** Refer to Table 5 in article. Authors conclusion: "In analysis of cognitive decline, findings were generally consistent with those of initial cognitive function; however, results were somewhat weaker, likely due to the short period over which we measured decline." Odds ratios of cognitive decline according to educational attainment: RN: 1.0 (ref): LPN/LVN: 1.1 (0.8–1.5)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			diabetes, postmenopausal hormone use, history of depression, and income Age Smoking Physical activity Alcohol **Method(s) of assessing cognitive status:** Cognitive function assessed using TICS, a validated telephone battery, plus 4 other cognitive tests: East Boston Memory test (immediate and delayed recalls); Delayed word recall; Category fluency. Summary composite score calculated from all 5 tests. <u>Cognitive impairment and decline</u> defined as worst 10% of test distribution. **Informant interview?** No	2-yr AD: 0.9 (0.6–1.4) BA or BS: 1.0 (0.8–1.3) Masters: 1.0 (0.8–1.4) Doctoral: 0.7 (0.4–1.2) After controlling for covariates, there was no statistically significant association between level of education and cognitive decline.	
Lee,	**Geographical**	**Age:**	**Risk factor/exposure**	**1) Follow-up rate:**	**Comments:**

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Kawachi, Berkman, et al., 2003 Nurses Health Study	**location:** U.S. **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 22,213 contacted. 19,510 (88%) completed baseline interview. 15,594 **Duration of follow up:** 2 years **Time from risk factor assessment to final cognitive assessment:** 2 yrs	Mean: 74 yrs. **Sex:** Female: 19,319 (100%) Male: 0 **Race/ethnicity:** NR **Baseline cognitive status:** No exclusion by cognitive function **Inclusion criteria:** Nurses' Health Study participants aged 70 yrs or more who were free of diagnosed stroke and had answered the most recent mailed questionnaire. **Exclusion criteria:** Less than 15 years of education.	**1:** Education **Method of assessing risk factor/exposure 1:** Self-report 3 categories: 1) 3-year RN diploma (77.9%) 2) Bachelor's degree (16.4%) 3) Master's/doctoral degree (5.7%) **Covariates/potential confounders adjusted for in analyses:** Baseline test scores Age Clinical variables Medications Smoking Alcohol BMI SF-36 vitality and mental health scores **Method(s) of assessing cognitive status:** Cognitive function assessed using TICS, a validated telephone battery, plus 5 other cognitive tests: East Boston Memory test (immediate and delayed recalls);	22,213 were contacted at baseline. 19,510 (88%) completed the interview (7% refused, and 5% not reached because of inaccurate contact information). 19,319 completed baseline interview. 15,594/19,319 = 80.7% (but f/u was still ongoing at time of this analysis). 13,429 women (69.5%) had complete data for cognitive decline analyses. **2) Important baseline differences:** NA **3) Outcome of interest #1—cognitive decline** "We found statistically significant trends of decreasing odds of cognitive decline with increasing level of education on all six tests." <u>Global change score OR (95% CI):</u> 1) RN: 1.0 2) Bachelor's: 0.80 (0.68,0.94) 3) Master's/doctorate: 0.65 (0.50, 0.86) **4) Outcome of interest #2—cognitive tests as continuous data** "Comparable results; we found statistically significantly less mean decline on five tests for women with advanced graduate degrees, and statistically significant trends of decreasing mean decline with increasing education after multivariate adjustment."	None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Delayed word recall; Verbal fluency; Digit span backwards test. Global score calculated from all 6 tests. Low scorers defined as <31 points on the TICS. For remaining tests, low score defined as worst 10% of test distribution. Change scores calculated for each test, including global score. Cutpoints defined for each test. **Informant interview?:** No		
Li, Higdon, Kukull, et al., 2004 Adult Changes in Thought (ACT)	**Geographical location:** Seattle, WA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2581	**Age:** Mean (SD): 75.1 (6.1) **Sex:** Female: 1409 (59.8%) Male: 947 (40.2%) **Race/ethnicity:** White 2149 (91.2%) Non-White 206 (8.7%) Missing 1 (0.04%) **Baseline cognitive**	**Risk factor/exposure 1:** Statin 0 one statin equivalent = 10 mg simvastatin, or 20 mg lovastatin or pravastatin, or 5 mg atorvastatin with use defined as at least 2 consecutive fills within a 6-month period **Method of assessing**	**1) Follow-up rate:** 2356 (91.3%) 392 statin users (41 demented; 351 non-demented) 1964 non-statin (271 demented; 1693 non-demented) 168 with AD; 48 possible AD; 96 other dementia (69% AD/possible AD) Unadjusted HR for probable AD (95% CI)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Yes 4) Adequate description of the

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		status:	**risk factor/exposure 1:**	No statin 1.0 (ref)	cohort? Yes
	Duration of follow up: ~ 17 yrs	Non-demented	Other – pharmacy record	Statin 0.90 (0.54 to 1.51)	5) Validated method for ascertaining exposure? Yes
	Time from risk factor assessment to final cognitive assessment: Variable	**Inclusion criteria:** Group Health Cooperative HMO member; ≥ 65 yo	**Risk factor/exposure 2:** Age, sex, medical history, family history	Adjusted HR for probable AD (95% CI) – age, education, APOE-e4 status an use of other lipid lowering agents	6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
		Exclusion criteria: Cognitive Abilities Screening Instrument (CASI) score < 86	**Method of assessing risk factor/exposure 2:** Self-report	No statin 1.0 (ref) Statin 0.82 (0.46 to 1.46) No dose response relationship. Adjusted HR analyzed by cumulative equivalent dose (<1,461 s >=1,451 equivalents), duration (< 2 years vs >= 2years) or average daily equivalent dose (<4 vs. >= 4 equivalents/day) showed overlapping confidence intervals.	
			Covariates/potential confounders adjusted for in analyses: status Age at entry Yrs of education APOE e4 status Use of other lipid lowering agents	CEQ < 1,461 0.95 (0.46 to 1.97); >= 1,461 (0.73 (0.26 to 2.05) Duration < 2 years 0.91 (0.40 to 2.09); >= 2 years 0.87 (0.31 to 2.47) ADED < 4 0.91 (0.40 to 2.09); >= 4 0.63 (0.21 to 1.91)	
			Method(s) of assessing cognitive status: Other – CASI screen and if < 86, clinical exam, lab test, neuroimaging and neuropsychological testing; Dx assigned using NINCDS-ADRDA		
			Informant interview?: No		

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Li, Rhew, Shofer, et al., 2007 Adult Changes in Thought (ACT)	**Geographical location:** Seattle, WA **Setting:** Community – cohort from health maintenance organization **Study design:** Prospective cohort **Number of participants enrolled:** 2581 2356 analyzed **Duration of follow up:** Baseline (and exposure) 1994-6 then biennially through end of 2004. CASI each follow up; mean f/u duration NR **Time from risk factor assessment to final cognitive assessment:** up to 10 years	**Age:** Range: Age 65-69 542 (23%) Age 70-74 730 (31%) Age 75-79 565 (24%) Age 80-84 353 (15%) Age 85+ 166 (7%) **Sex:** [n (%)] Female: 1414 (60%) Male: 942 (40%) **Race/ethnicity:** [n (%)] White 2144 (91%) African-Amer 94 (4%) Other 94 (4%) Info missing 24 (1%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Member of community-based, large HMO; age >=65; selected randomly; dementia-free; non-nursing home resident; agree to prticipate (48% of eligibles) and at least one follow-up **Exclusion criteria:** NR other than above	**Risk factor/exposure 1:** htn with sbp high ≥ 160, borderline 140-159, dbp high ≥ 90, borderline 80-89. Enrollment bp considered primary exposure **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Race (white/nonwhite), Sex, years education, presence of at least one apoE4, (hx cad, cvc, dm, use of antihypertensives), analyses were done but paratmeter estimates not reported for AD, just nonspecific dementia Separate models for three age strata: 65-74, 75-84, older because of significant interaction term for HTN*age **Method(s) of**	**1) Follow-up rate:** of the 48% of the initial eligible who participated 91% had at least one follow up. **2) Important baseline differences:** in hypertensive group, more females, diabetics and use of antihypertensives **3) Outcome of interest #1** Incident dementio =380 (AD = 204) HR for Ad with sbp ≥ 160 compared to <140 age 65-74 1.38 (95% CI 0.71-2.70) age 75-84 0.94 (0.62-1.42) ≥85 0.70(0.25-1.95) HR for Ad with sbp 140-159 compared to < 140 age 65-74 1.47 (95% CI 0.80-2.71) age 75-84 0.60 (0.38-0.92) ≥85 0.48 (0.15-1.57) **4) Outcome of interest #2** HR for AD with dbp ≥ 90 compared to dbp < 80 age 65-74 0.82 (95% CI 0.29-2.35) 75-84 0.73 (0.34-1.59) 85+ no cases HR for AD with dbp 80-89 compared to dbp < 80 age 65-74 1.71 (95% CI 0.98-2.97) 75-84 0.96 (0.63-1.47) 85+ 1.58 (0.58 – 4.29) Additional analyses that adjusted for additional covariates (hx cad, cvc, dm, use of antihypertensives), analyses were reported to produce	**Comments:** Question 1 Dementia eval triggered by casi score < 86. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			assessing cognitive status: NINCDS-ADRDA DSM-IV **Informant interview?:** No	little change in the risk estimates	
Lindsay, Laurin, Verreault, et al., 2002 Canadian Study of Health and Aging (CSHA)	**Geographical location**: Eighteen field centers across all Canadian provinces. **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** Community sample:9008 Eligible subjects:7273 Enrolled subjects:6434 Final study sample:4615 **Duration of follow up:** 5 yrs **Time from risk factor assessment to final cognitive assessment:** 5 yrs	**Age:** Case/Control Mean (SD): 81/72.9 Median::87/78 Range: 69-105 yrs/ 70-100 yrs **Sex:** Case/control Female: 131 (67.5%)/ 2239(57.5%) Male: 63(32.5%)/ 1655(42.5%) **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** 65 yrs and older **Exclusion criteria:** NR	**Risk factor/exposure 1:** ApoE4 **Method of assessing risk factor/exposure 1:** Direct measurement **Risk factor/exposure 2:** High blood pressure **Method of assessing risk factor/exposure** Self report Direct measurement **Risk factor/exposure 3:** Depression **Method of assessing risk factor/exposure** Self report **Risk factor/exposure 4:** Prior head injury **Method of assessing risk factor/exposure**	**1) Follow-up rate:** 4615/6434 (71.7%) participated in follow up study **2) Important baseline differences:** NA **3) Outcome of interest #1--APOE** Odds ratio(OR) 3.28 (95% CI: 1.98,5.44) **4) Outcome of interest #2—High BP** OR 0.88(0.62,1.27) **5) Outcome of interest #3--Depression** OR 1.44(0.84,2.48) **6) Outcome of interest#4—Prior head injury** OR 0.87 (0.56,1.36) **7) Outcome of interest#5--Diabetes** OR 1.03 (0.58,1.84) **8) Outcome of interest #6—Antihypertensive agents** OR 0.91 (0.64,1.30) **9) Outcome of interest#7—Any NSAIDs**	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Self report **Risk factor/exposure 5:** Diabetes **Method of assessing risk factor/exposure** Self report **Risk factor/exposure 6:** Antihypertensive agents **Method of assessing risk factor/exposure** Self report **Risk factor/exposure 7:** Any NSAID use **Method of assessing risk factor/exposure** Self report **Risk factor/exposure 8:** Estrogen replacement therapy(ERT) **Method of assessing risk factor/exposure 8:** Self-report **Covariates/potential confounders adjusted for in analyses:**	OR 0.65 (0.44,0.95) **10)Outcome of interest#8—Estrogen replacement therapy** OR 1.37 (0.48,3.95) **11) Years of Education (controlled for age and sex) with ≥13 years as reference.** 9-12 yrs: OR 1.37 (95% CI: .91,2.06) 0-8 yrs: OR 1.90 (95% CI: 1.25,2.90) Analysis included 194 AD cases and 3894 cognitively normal controls. Increased risk of AD was associated with ApoE4 while NSAID use was associated with reduced risk of AD. No statistically significant association was found for history of depression, estrogen replacement therapy, high blood pressure, head trauma, antihypertensive use, diabetes.	

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Age Race Sex Educational level Baseline cognitive status Wine consumption Coffee consumption Medical conditions(arthritis, cancer, thyroid, PUD) Family history AD Vascular disease Tobacco use **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM-4th edition Other – NINDS-AIREN Modified Mini- Mental State Exam(3MS)(screening criteria: positive result <78/100) **Informant interview?:** Yes		
Lu, Edland, Teng, et al., 2009 Alzheimer's Disease Cooperative Study	**Geographical location:** 69 ADCS sites in US & Canada **Setting:** Clinical – participants in the Alzheimer's Disease Cooperative	**Age:** Mean (SD): Depressed 73.11 (7.32) Non-depressed 72.83 (7.31) Range: 55-91 years **Sex:** [n (%)]	**Risk factor/exposure 1:** Depression **Method of assessing risk factor/exposure 1:** Beck Depression Inventory (BDI)	**1) Follow-up rate:** 756/769 (98%) **2) Important baseline differences:** N/A **3) Outcome of interest #1** Impact of risk factor on progression to AD	**Comments:** Question 4 Note: This represents a secondary analysis of an RCT, with data pooled across all three treatment arms (donepezil vs. vitamin E vs. placebo), with adjustment for treatment arm in the Cox model.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
drug trial	Study drug trial **Study design:** RCT (though analyzed as if it were an uncontrolled observational study) **Test intervention** Vitamin E (2,000 IU) OR Donepezil (10mg) **Comparator intervention(s)** Matching placebo **Number of participants enrolled:** 756 208 Depressed 548 Non-depressed **Duration of follow up:** 3 years **Time from risk factor assessment to final cognitive assessment:** 3 years	Female: Depressed 104 (50%) Non-depressed 241 (44%) Male: Depressed 104 (50%) Non-depressed 307 (56%) **Race/ethnicity:** [n (%)] White Depressed 193 (93%) Non-depressed 504 (92%) **Baseline cognitive status:** aMCI **Inclusion criteria:** Met criteria for aMCI of a presumably degenerative nature (insidious onset, gradual progression), defined as 1) subjective memory complaint corroborated by an informant, 2) insufficient global cognitive and functional impairment to meet National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease	**Risk factor/exposure 2:** APOE genotype **Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Baseline MMSE score APOE genotype Treatment group NYU paragraph delayed recall score **Method(s) of assessing cognitive status:** NINCDS-ADRDA When the clinical diagnosis of AD was made, all cognitive and functional data were sent to the ADCS Coordinating Center and forwarded to a 5-member central review committee for a consensual diagnosis. **Informant interview?:** No	BDI score: HR 1.03 (95% CI: 1.01, 1.06; p=0.022) APOE carrier: HR 2.03 (95% CI: 1.45, 2.83; p<0.0001)	**Quality assessment:** *For observational studies (although data are from an RCT, they are analyzed as though this were an uncontrolled observational study):* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD, 3) Logical Memory (one paragraph) delayed recall score 1.5 SD below education-adjusted normative means, 4) Clinical Dementia Rating (CDR) score of 0.5, and 5) Mini-Mental State Examination (MMSE) score ≥ 24. **Exclusion criteria:** Score of greater than 12 on the Hamilton Depression Rating Scale (HAM-D) or a modified Hachinski score of >4; h/o significant cerebrovascular disease; CNS infarct, infection, or focal lesions of clinical significance on CT or MRI; medical or psychiatric conditions that could interfere with study participation; pregnancy, lactation, or childbearing potential; or taking vitamins or other supplements (may take stable doses at least 1 month prior to screening of antidepressants			

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		lacking significant anticholinergic side effects.			
Luchsinger, Honig, Tang, et al., 2008 WHICAP	**Geographical location:** Northern Manhattan, NYC, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1,128 in parent study; 526 in current analysis **Duration of follow up:** 5.1 (3.3) years **Time from risk factor assessment to final cognitive assessment:** 5.1 (3.3) years	**Age:** Mean (SD): 75.1 (6.4) **Sex:** [n (%)] Female: 356 (67.7%) Male: 170 (32.3%) **Race/ethnicity:** [n (%)] AA 31.2% Hispanic 48.3% White 20.5% **Baseline cognitive status:** Non-demented **Inclusion criteria:** Medicare recipient selected at random Age >=65 HAMD at baseline At least one f/u **Exclusion criteria:** Dementia	**Risk factor/exposure 1:** Depression – Hamilton Depression Rating Scale – 17-item **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level APOE-e4 DM HTN Heart disease Current smoking Stroke **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** No	**1) Follow-up rate:** 50.2% >= 4 f/u visits 9.7% 3 f/u visits 17.5% 2 f/u visits 22.6% 1 f/u visit Unknown with 0 visits in the overall cohort **2) Important baseline differences:** NR **3) Outcome of interest #1** HAMD = 0, 8 AD cases, HR 1.0 HAMD = 1 to 9, 83 cases, HR 2.3 (1.0 to 5.3) HAMD >9, 23 AD cases, HR 3.0 (1.2 to 7.9)	**Comments:** Only a convenience sample of overall cohort completed the HAMD and they differed systematically (younger, more DM, hearts disease, stroke) than those not completing the HAMD **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Partial 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the cohort: Yes 5) Validated method for ascertaining exposure: Yes 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Yes 9) Completeness of follow-up: Can't Tell 10) Analysis controls for confounding: Yes 11) Analytic methods appropriate: Yes
Luchsinge	**Geographical**	**Age:**	**Risk factor/exposure**	**1) Follow-up rate:**	**Comments:**

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
r, Reitz, Honig, et al., 2005 WHICAP	**location:** northern Manhatten, NY **Setting:**] Community **Study design** Prospective cohort **Number of participants enrolled:** 2126 initial screened cohort; 1138 final cohort **Duration of follow up:** Follow up data were collected ~ every 18 months through ~5 yrs. (6292 person-year follow up) **Time from risk factor assessment to final cognitive assessment:** Mean 5.5 yrs(SD 3.2 person years)	Mean (SD): 76.2(5.9) **Sex:** Female: 734(69.8%) Male: 404(40.2%) **Race/ethnicity:** Black: 377(33.1%) Hispanic: 505(44.4%) White: 256(22.5%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** 65 yrs and older, non-demented **Exclusion criteria:** NR	**1:** Diabetes Mellitus **Method of assessing risk factor/exposure 1:** Self-report Other – Use of specific DM medications **Risk factor/exposure 2:** Hypertension **Method of assessing risk factor/exposure 2:** Self-report **Risk factor/exposure 3:** Tobacco use(current vs past) **Method of assessing risk factor/exposure 3:** Self report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status Vascular disease Lipid values	1012/1138(88.9%) 126 excluded as they were missing *APOE4* genotyping. **2) Important baseline differences:** NA **3) Outcome of interest #1** At risk, n=36; cases n=11(30.6 %) HR 3.8(1.8,8.2) At risk: n=306; cases n=48(15.7%) HR 1.5(0.9,2.4) **4) Outcome of interest #2—Probable and possible AD (n=246), by risk factor** Hazard ratio (95% CI) Diabetes: 3.8 (1.8, 8.2) HTN: 1.5 (0.9, 2.4) Tobacco: 2.2 (1.0, 4.9) **5) Outcome of interest #3** At risk: 41; cases n=9(21.9) HR2.2(1.0,4.9) All data utilized model 2 which adjusted for age, sex, ethnic group, education and *APOE*4.Sample size 1012 due to 126 missing *APOE* genotyping All CI :95% Authors' conclusion: "The risk of AD increased with the number of vascular risk factors, diabetes, HTN, heart disease, and current smoking. We also found that different combinations of risk factors	None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			BMI **Method(s) of assessing cognitive status:** NINCDS-ADRDA Other-Clinical Dementia Rating(>0.5) **Informant interview?:** No	were associated with a high risk of AD. Diabetes and smoking were the strongest risk factors."	
Luchsinger, Tang, Miller, et al., 2007 WHICAP	**Geographical location:** Northern Manhattan,NY **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 965 **Duration of follow up:** 6.1 (3.3) yr **Time from risk factor assessment to final cognitive assessment:** 6.1 (3.3) yr	**Age:** Mean (SD): 75.8 (5.8) **Sex:** [n (%)] Female: 680 (70.5) Male: 285 (29.5) **Race/ethnicity:** [n (%)] AA 315 (32.6) White 213 (22.1) Hispanic 437 (45.3) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Medicare recipients age ≥65 residing in Northern Manhattan **Exclusion criteria:** None	**Risk factor/exposure 1:** Folate, Vit B6 & B12 **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level APOE DM HTN Smoking Heart disease Stroke **Method(s) of assessing cognitive status:** NINCDS-ADRDA	**1) Follow-up rate:** 965/1375 (denominator excludes those with dementia, but don't know how much attrition due to death) **2) Important baseline differences:** Ind who dev AD were older, less educated. A higher proportion of Hispanics and a lower proportion of whites dev AD. A higher proportion w/ DM, HTN, heart disease and stroke dev AD. **3) Outcome of interest #1** Folate: Higher quartiles of intake were not significantly associated with risk of AD B6: Higher quartiles of intake were not significantly associated with risk of AD B12: Higher quartiles of intake were not significantly associated with risk of AD	**Comments:** Question 1 The association between folate and AD became significant when also controlled for B 6 & B12 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			DSM **Informant interview?:** No		confounding? Yes 11) Analytic methods appropriate? Yes
Luchingser, Tang, Shea, et al., 2002 WHICAP	**Geographical location:** Northern Manhattan,NY **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 980 **Duration of follow up:** 4 (1.5) **Time from risk factor assessment to final cognitive assessment:** 4 (1.5)	**Age:** Mean (SD): 75.3 (5.8) **Sex:** [n (%)] Female: 657 (67) Male: 323 (33) **Race/ethnicity:** [n (%)] AA 314 (32) White 245 (25) Hispanic 421 (43) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Medicare recipients age ≥65 residing in Northern Manhattan **Exclusion criteria:** NR	**Risk factor/exposure 1:** caloric intake, carbohydrates, fats, protein **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level APOE **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** No	**1) Follow-up rate:** 980/1192 (1192 includes those lost to follow-up only, not those excluded due to dementia) **2) Important baseline differences:** Total calories: highest quartiles older and more education Carbohydrates: Highest quartiles older, less likely to be female, Protein: highest quartiles less education **3) Outcome of interest #1** Total daily calories: quartile 4 assoc with increased risk of AD (HR: 1.48; 1.00-2.19) Carbohydrates: no assoc with AD Fats: no assoc with AD Protein: no assoc with AD **4) Outcome of interest #2** Only APOE 4 positive associated with risk of AD for: Total calories: quartile 4 (HR 2.27 (1.11-4.68) Fats: quartile 4 (HR: 2.31; 1.09-4.89)	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Luchsinger, Tang, Shea, et al., 2003	**Geographical location:** Northern Manhattan,NY	**Age:** Mean (SD): Mean (SD): 75.3 (5.8)	**Risk factor/exposure 1:** Vit C & E and carotenoids	**1) Follow-up rate:** 980/1192 (1192 includes those lost to follow-up only, not those excluded due to dementia)	**Comments:** Question 1 **Quality assessment:**

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
WHICAP	**Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 980 **Duration of follow up:** 4 (1.5) **Time from risk factor assessment to final cognitive assessment:** 4 (1.5)	**Sex:** [n (%)] Female: 657 (67%) Male: 323 (33%) **Race/ethnicity:** [n (%)] AA 314 (32) White 245 (25) Hispanic 421 (43) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Medicare recipients age ≥65 residing in Northern Manhattan **Exclusion criteria:** NR	**Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level APOE Smoking **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** No	**2) Important baseline differences:** Vit C & E users had more education Lower proportion of Hispanics were Vit E users **3) Outcome of interest #1** Calorie adjusted intake (no-supplements) Carotenoids: higher intake quartiles no assoc with AD Vit C: higher intake quartiles no assoc with AD Vit E: higher intake quartiles no assoc with AD **4) Outcome of interest #2** Supplemental and dietary intake Vit C: Highest intake quartile no assoc with AD Vit E: Highest intake quartile no assoc with AD	*For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Luchsinger, Tang, Shea, et al., 2004 WHICAP	**Geographical location:** New York City, NY **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2126 original subjects 909 sample for this	**Age:** Median: 77 years **Sex:** Female: 70% Male: 30% **Race/ethnicity:** Hispanic 52% African American 30% White 18% **Baseline cognitive status:** Non-demented	**Risk factor/exposure 1:** hcy **Method of assessing risk factor/exposure 1:** Direct measurement Frozen fasting plasma, doesn't say how long it was stored. **Covariates/potential confounders adjusted for in**	**1) Follow-up rate:** subset who had a follow up and hcy levels seem to have been chosen. **2) Important baseline differences:** Subjects with higher hcy were older, more men, less dm, more stroke, more prevalent dementia, more prevalent AD. **3) Outcome of interest #1** When unadjusted those in the highest quartile of hcy as compared to the lowest quartile had hr for ad of 2.0 (1.2 – 3.5). When adjusted for	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Yes 4) Adequate description of the cohort? Yes 5) Validated method for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	study 679 available for longitudinal analysis **Duration of follow up:** I can't tell. Plasma reportedly drawn at baseline. Cog testing done every 18 mos. Reportedly 3,206 person years. Can we assume a mean follow up of 4.7 yrs per person? **Time from risk factor assessment to final cognitive assessment:** hcy at baseline. Follow ups every 18 mos.	**Inclusion criteria:** Medicare recipients Residents of Washington Heights community in NYC **Exclusion criteria:** Dementia	**analyses**: age, sex, education, apoE4, stroke **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** No	age, sex, education, apoE4, stroke hr was 1.3 (0.8 – 2.3)	ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Can't Tell 9) Completeness of follow-up? Partial 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Lytle, Vander Bilt, Pandav, et al., 2004 MoVIES	**Geographical location:** Southwestern Pennsylvania, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1146 **Duration of follow up:** 2 yrs	**Age:** Mean (SD): 76.8 (5.3) **Sex:** [n (%)] Female: 722 (63%) Male: 424 (37%) **Race/ethnicity:** White: 97.7% Non-white: 2.3% **Baseline cognitive status:** All **Inclusion criteria:** 65 yrs or older, living in the community, fluent	**Risk factor/exposure 1:** Exercise. **Method of assessing risk factor/exposure 1:** Self-report Subjects were asked whether they engaged in an exercise program, and, if so, in what type of exercise, exercise equipment used, and freq. and duration of exercise.	**1) Follow-up rate:** Analytical sample 929 Attrition rate due to death 9 – 14% Attrition due to other causes 2.8% **2) Important baseline differences:** There was a statistically significant difference in age and sex among the high, low, and no exercise groups at baseline **3) Outcome of interest #1** High exercise level at wave 3 was associated with reduced risk of cognitive decline at wave 4. OR: 0.39, (95%CI 0.19, 0.78) **4) Outcome of interest #2**	**Comments:** None Analysis included subjects with baseline cognitive impairment **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Time from risk factor assessment to final cognitive assessment: 2 yrs	in English, and having at least a 6th grade education. **Exclusion criteria:** NR	Aerobic vs. non-aerobic **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Self rating of health **Method(s) of assessing cognitive status:** Cognitive battery, including the MMSE and a standardized risk factor and outcome assessment questionnaire. Cognitive decline defined as "being in the 90th percentile of decline in this cohort, ie, declining by 3 or more MMSE points during the 2-year interval between assessments." **Informant interview?** No	When high exercise was considered as exercising for more than 5 or more days a week for at least 30 minutes, cognitive decline was negatively associated with high exercise. OR: 0.45, (95%CI 0.22, 0.95) Low exercise also showed a negative association. OR:0.63, (95%CI 0.39, 0.997 **Outcome of interest #3** Wave 3 mmse was not associated with future exercise level. This analysis was done to examine both directions of the relationship.	ascertaining exposure? No 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Manly, Schupf, Tang, et al., 2005 WHICAP	**Geographical location:** Northern Manhattan NY, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1362 **Duration of follow up:** Approximately 4.5 years. Not reported specifically. **Time from risk factor assessment to final cognitive assessment:** Approximately 4.5 years. Not reported specifically.	**Age:** Mean (SD): High education: 75.5 (6.2) Low education: 75.9 (5.9) **Sex:** [n (%)] High education: Female: 67.1% Male: 32.9% Low education: Female: 69.8% Male: 30.2% **Race/ethnicity:** [n (%)] High education: White 73.6% Low education: White 26.4% **Baseline cognitive status:** Normal Non-demented **Inclusion criteria:** English as primary language, self identified as Hispanic, African American or Non-Hispanic White. **Exclusion criteria:** Stroke, Parkinson's disease Cognitive or functional impairment at baseline.	**Risk factor/exposure 1:** Reading Level **Method of assessing risk factor/exposure 1:** Self-report Direct measurement - Wide Range Achievement Test Version-3 **Risk factor/exposure 2:** Literacy, education **Method of assessing risk factor/exposure 2:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level **Method(s) of assessing cognitive status:** CDR DSM IV **Informant interview?:** No	**1) Follow-up rate:** Of 1362 in current study, 80 were dead, 94 refused and 75 moved out of the area. 111 had missing data. 1002/1113= 90.02% **2) Important baseline differences:** High education group was more likely to be White, have more years of education, have higher reading level, and follow up longer. **3) Outcome of interest #** After controlling for age, gender, race and education, participants with lower literacy were more likely to have faster decline in cognition. Memory: β= 3.2; p= .002 Executive function: β= 1.0; p= 0.002 Language: β= 0.2; p= .000	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Can't Tell 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Martin, Szekely, Brandt, et al., 2008 ADAPT	**Geographical location:** Baltimore, MD Boston, MA Rochester, NY Seattle, WA Sun City, AZ Tampa, FL **Setting:** Community **Study design:** RCT **Test intervention** Celecoxib 200mg 2x/day OR naproxen sodium 220mg 2x/day **Comparator intervention(s)** placebo **Number of participants enrolled:** 2528 **Duration of follow up:** celecoxib 736 dys, naproxen 737 dys, placebo 736 dys **Time from risk factor assessment to final cognitive assessment:** Up to 3 yrs of annual cognitive assessments	**Age:** Median: 74 Range: 70 - 90 **Sex:** [n (%)] Female: 1160 (45.9%) Male: 1368 (54.1%) **Race/ethnicity:** [n (%)] White 2452 (97.0%) African American 38 (1.5%) Hispanic 18 (0.7%) Other 20 (0.8%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 70 yo; have at least 1 first-degree relative with AD-like dementia, score satisfactorily on eligibility test battery for excluding cognitive impairment **Exclusion criteria:** Regularly use NSAIDS (but aspirin use of 81 mg/day allowed)	**Risk factor/exposure 1:** RCT with celecoxib, naproxen, placebo **Method of assessing risk factor/exposure 1:** This is an rct. The nsaid was given to subjects. **Covariates/potential confounders adjusted for in analyses:** NR **Method(s) of assessing cognitive status:** change in test scores over time. **Informant interview?:** No	**1) Follow-up rate:** see comments **2) Important baseline differences:** none are obvious **3) Outcome of interest #1** Whether an ITT analysis or if censored after drug terminated,, scores of 3MS were significantly lower in both treatment groups than in placebo. **4) Outcome of interest #2** use of naproxen or celecoxib did not improve cognitive function. Weak evidence fro detrimental effect of naproxen.	**Comments:** Trial terminated early because of celecoxib 41% terminated drug, 19% lost to follow up, naproxen 42% terminated drug, 20% lost to follow up, placebo 38% terminated drug, 21% lost to follow up This group also reports on incident dementia in the other ADAPT publication. *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Partial 6) Differential dropout rate < 10%? Can't Tell 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Masaki, Losonczy, Izmirlian, et al., 2000 HAAS	**Geographical location:** Oahu, Hawaii **Setting:** Community (some in nursing homes) **Study design:** Prospective cohort **Number of participants enrolled:** 3385 **Duration of follow up:** 3-5 yr **Time from risk factor assessment to final cognitive assessment:** 3-5 yr for main analyses (sub-group of long term users 11-13 yr)	**Age:** Mean (SD): Non-demented 73.9 Demented 78.6 **Sex:** [n (%)] Female 0 (0%) Male: 3385 (100%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Men of Japanese ancestry born between 1900 and 1919 who resided on the island of Oahu, Hawaii in 1965 and were participants of the Honolulu Heart Program. **Exclusion criteria:** NR	**Risk factor/exposure 1:** Vit E and C **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Educational level Childhood years spent in Japan APOE Hx of stroke **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM CASI **Informant interview?:** Yes	**1) Follow-up rate:** 3385/3682 (denominator excludes those thought to be demented at time of nutrition data collection) 91.93% **2) Important baseline differences:** Nondemented were younger, more education, less time during childhood in Japan Some differences (age) reported are at the time of the dementia diagnosis (not really baseline) **3) Outcome of interest #1** No association between AD and vitamin E or C use C w/o E: OR-1.61 (0.67-3.87) E w/o C: OR 0.84 (0.19-3.77) E and C use: OR – 1.81 (0.91-3.62)	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Maxwell, Hicks, Hogan, et al., 2005 CSHA	**Geographical location:** British Columbia, Prairie Provinces, Ontario, Quebec, Atlantic Provinces, Canada	**Age:** Mean (SD): 78.1 (6.8) **Sex:** [n (%)] Female: 572 (64) Male: 322 (36)	**Risk factor/exposure 1:** Vit E and C supplements, including multi-vitamins **Method of assessing**	**1) Follow-up rate:** 94/1084 (denominator excludes 698 not followed due to death) **2) Important baseline differences:** Vitamin users were older, less likely to have hx of heavy smoking, more	**Comments:** Question 1 & 2 This is on a very select subset of the CSHA sample – those at very high risk of being cognitively impaired, including the institutionalized.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Setting: Community (included residents of institutions) **Study design:** Prospective cohort **Number of participants enrolled:** 894 **Duration of follow up:** Approx 5 yrs **Time from risk factor assessment to final cognitive assessment:** Approx 5 yrs	**Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Representative sample of Canadians ≥ 65 yr from the 5 regions noted above For present analyses included only those who completed a clinical exam at baseline and were not demented. Those who completed the clinical exam: ≤ 78 on 3MS, random sample of those scoring >78 on 3MS, those who could not be screened and all institutionalized subjects **Exclusion criteria:** NR	**risk factor/exposure 1:** Self-report Medical record – institutionalized subjects **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Blood pressure Baseline cognitive status Institutional residence **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM Other – Cog decline= decrease ≥ 10 points on 3MS from Time 1 to Time 2 **Informant interview?:** No	likely to lower serum albumin levels **3) Outcome of interest #1** Cognitive decline: Vit E and C and/or multivitamin use assoc with lower risk of cognitive decline (OR – 0.51, 0.29-0.-0.90) Any vitamin use assoc with lower risk of cognitive decline (OR – 0.57; 0.34-0.93) Vit E alone was not assoc with cognitive decline (OR-0.64 (0.08-5.41) Vit C alone was not assoc with cognitive decline (OR – 0.83 (0.29-2.39) **4) Outcome of interest #2** Any vitamin use not assoc with risk of AD (OR-1.00 (0.53-1.87)	Source for risk factor exposures was different for community and institutionalized subjects. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? No 2) Selection minimizes baseline differences in prognostic factors? No 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
McMahon, Green, Skeaff, et al., 2006 (New Zealand Homocystei	**Geographical location:** Dunedin, New Zealand **Setting:** Community **Study design:**	**Age:** Median: 73 years **Sex:** Female: 65 (52%) in placebo group Female: 47 (37%) in vitamin group	**Risk factor/exposure 1:** hcy **Method of assessing risk factor/exposure 1:** Direct measurement	**1) Follow-up rate:** For purposes of analysis – 91.3% in placebo group, 92.0% in vitamin group. In placebo group, 12 were lost to follow up, and 7% dc'd intervention but stayed in study. In vitamin group, 11 were lost to	**Comments:** Question 5 rct in cognitive decline **Quality assessment:** 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
ne)	RCT **Test intervention:** Folate 1000 micrograms per day Vitamin B12 500 micrograms per day Vitamin B6 10 milligrams per day **Comparator intervention(s):** Placebo **Number of participants enrolled:** 465 assessed for eligibility 276 randomized 253 analyzed **Duration of follow up:** follow ups done at 1 and 2 yrs. **Time from risk factor assessment to final cognitive assessment:** 2 yrs	Male: 61 (48%) in placebo group Male: 80 (63%) in vitamin group **Race/ethnicity:** NR **Baseline cognitive status:** didn't have "suspected dementia" all but five had mmse ≥ 26, mean baseline mmse > 29 **Inclusion criteria:** ≥ 65 years **Exclusion criteria:** Suspected dementia Taking meds known to interfere with folate metabolism Taking vitamin supplements containing folic acid, B12, or B6 Being treated for depression Diabetic History of stroke or TIAs	Fasting plasma, only those >13 µmol/l of hcy were eligible **Covariates/potential confounders adjusted for in analyses:** Sex, education, baseline cognitive scores. **Method(s) of assessing cognitive status:** change in test scores **Informant interview?:** No	follow up, and 8 dc'd intervention but stayed in study. **2) Important baseline differences:** more women and lower cholesterol in the placebo group. **3) Outcome of interest #1** For the combined testing score, the vitamin group was -0.11 std dev scores WORSE than the placebo group. **4) Outcome of interest #2** 1 and 2 yrs change scores were given for each test. The only significant findings in the fully adjusted models was on Trails B for which the mean time to completion was 8% longer in the treatment group (the exponent of the difference between the log-transformed values =1.08; 95% confidence interval1.02 -1.14)	assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes
McNeill, Avenell, Campbell, et al., 2007 MAVIS	**Geographical location:** 6 centers in Northeast Scotland **Setting:**	**Age:** Median: Suppl 72 Placebo 71 Range: Suppl 68.0 – 76.0	**Risk factor/exposure 1:** Single tablet containing 11 vitamins and 5 minerals taken daily for 12 months.	**1) Follow-up rate:** Of the 910 participants, over the course of the 1-year study, 12 died, 77 stopped taking their tablets and 44 were lost to follow-up.	**Comments:** None *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Trial	Clinical – Primary care health centers **Study design:** RCT **Test intervention** Supplement containing: 800 µg vitamin A, 60 mg vitamin C, 5 µg vitamin D, 10 mg vitamin E, 1.4 mg thiamin, 1.6 mg riboflavin, 18 mg, niacin, 6 mg pantothenic acid, 2 mg pyridoxine, 1 µg vitamin B12, 200 µg folic acid, 14 mg iron, 150 µg iodine, 0.75 mg copper, 15 mg zinc, and 1 mg manganese **Comparator intervention(s)** placebo **Number of participants enrolled:** 910 **Duration of follow up:** 1 year **Time from risk factor assessment to final cognitive assessment:** 1 year	Placebo 68.0 – 76.0 **Sex:** [n (%)] Female: 431 (47.3%) Male: **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** NR Authors state: "we did not exclude any participation on the basis of impaired cognitive function, though those with dementia were unlikely to volunteer or would have been excluded by their doctor." **Inclusion criteria:** ≥ 65 yo; had not taken vitamin, mineral, or fish oil supplements within 3 mos of recruitment (1 mo for supplements of water soluble vitamins other than vitamin B12) **Exclusion criteria:** Did not exclude any participants on basis of impaired cognitive function, though those with dementia were unlikely to volunteer, or would have been excluded by their doctor.	**Method of assessing risk factor/exposure 1:** RCT intervention **Covariates/potential confounders adjusted for in analyses:** NA (RCT) **Method(s) of assessing cognitive status:** Digit span forward and verbal fluency tests at start and end of intervention period. **Informant interview?:** No	Does not appear to be intent-to-treat analysis. Not clear how many participants were included in the final analysis. **2) Important baseline differences:** None **3) Outcome of interest #1—Digit span forward** No evidence of an effect of supplements **4) Outcome of interest #2—Verbal fluency** "No evidence of a beneficial effect on the whole study population but there was weak evidence for a beneficial effect of supplementation in the 2 pre-specified subgroups: 1) age ≥75 (n=290), mean difference 2.8 (95% CI: -0.6, 6.2) 2) increased risk of micronutrient deficiency (n=260), mean difference 2.5 (95% CI: -1.0, 6.1)	assessment? Yes 3) Subjects/providers blind? Yes - Subject; Can't Tell – Providers 4) Outcome assessors blind? Can't Tell 5) Incomplete data adequately addressed? Can't Tell. Analytic approach not described well. 6) Differential dropout rate < 10%? Can't Tell 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Mehta, Ott, Kalmijn, et al., 1999 The Rotterdam Study	**Geographical location:** Rotterdam, Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 6645 **Duration of follow up:** Average 2.1 (0.8) years. **Time from risk factor assessment to final cognitive assessment:** Average 2.1 (0.8) years	**Age:** Mean (SD): 68.9 (8.6) **Sex:** [n (%)] Female: 3927 (59.1) Male: 2718 (40.9) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non demented **Inclusion criteria:** >55 yrs of age Residents of Rotterdam **Exclusion criteria:** Dementia	**Risk factor/exposure 1:** Head Trauma **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Education **Method(s) of assessing cognitive status:** NINCDS-ADRDA and DSM **Informant interview?:** Yes	**1) Follow-up rate:** 6645/7046 94.31% (those not included in analyses were missing TBI info) **2) Important baseline differences:** Patient who developed AD were older, less educated and more likely to be women at baseline. **3) Outcome of interest #1** The relative risk of AD for head trauma with loss of consciousness after adjusting for age, sex and education was 0.8; 95% CI 0.4-1.9 **4) Outcome of interest #2** RR of AD for number of head traumas: 1 head trauma = 0.8 (0.3- 2.0) >1 head trauma = 1.0 (0.1-7.6) **5) Outcome of interest #3** RR of AD for period between head trauma and interview: ≤ 10 years= 1.4 (0.3-6.3) >10 years= 0.7 (0.2-1.8) **6) Outcome of interest #4:** After controlling for age sex and education, APOE did not interact with head trauma in incident AD.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? No 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Morris, Beckett, Scherr, et al., 1998	**Geographical location:** East Boston, MA **Setting:**	**Age:** Mean (SD): mean range across exposures: 72 -75 **Sex:** [n (%)]	**Risk factor/exposure 1:** Vit E and C supplement use	**1) Follow-up rate:** Notes 80% of survivors in selected sample completed f/u **2) Important baseline differences:**	**Comments:** Question 1 No vitamin C or E users among those who became demented – so comparison was based on predicted

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
East Boston Study	Community **Study design:** Prospective cohort **Number of participants enrolled:** 633 **Duration of follow up:** 4.3 yrs **Time from risk factor assessment to final cognitive assessment:** 4.3 yrs	Female: range across exposure groups 342-437 (54-69%) Male: 196-291 (31-46%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Stratified sample of residents of East Boston age > 65 yr in 1982-83. In 1985-86 fup, the stratified sample for clinical eval was weighted towards those who were older and had greater cog decline on screening measures **Exclusion criteria:** NR	**Method of assessing risk factor/exposure 1:** Self-report – limited to use in previous 2 wks **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Time to FUP Sample weight **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** No	Vitamin supplement users were more like to have at least some high school education. Vit E users were slightly younger. Multivitamin users more likely to be female and to have more than a H.S. educ **3) Outcome of interest #1** Fewer than expected incident AD cases used Vit C (p=0.04) No difference in expected AD incidence and observed incidence among Vit E users (p=0.23)	rate of AD **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? No –subsample targeted those at high risk of AD 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes (vitamin use in previous 2 wks) 6) Validated method for ascertaining clinical outcomes? Partial. No informant report. 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes. Ok (new stratified sample at fup) 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate?: Partial (used predicted incidence of AD rather than comparing observed incidence in two exposure groups)
Morris, Evans, Bienias, et al., 2004a CHAP	**Geographical location:** Chicago, IL **Setting:** Community	**Age:** For AD sample (815): Mean ranged from 71-73.2 across niacin exposure groups	**Risk factor/exposure 1:** Niacin **Method of assessing risk factor/exposure**	**1) Follow-up rate:** Difficult to get appropriate numbers 842/1249 new stratified random sample (authors reported 73.95% of survivors completed fup)	**Comments:** Reports continuous outcome for cog decline; also mentions categorical outcome but no results provided **Quality assessment:**

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Study design: Prospective cohort **Number of participants enrolled:** 3718 for cognitive decline 815 for incident AD **Duration of follow up:** Mean 3.9 yrs (for AD analyses) Says Median 5.5 yrs in abstract (appears to be cognitive decline analyses) **Time from risk factor assessment to final cognitive assessment:** 1041 - 2.7 yrs 3718 – 4.3 yr (these are estimates based on info in other papers)	**Sex:** [n (%)] NR in a format that is useful **Race/ethnicity:** [n (%)] NR in a format that is useful **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged ≥65 yrs **Exclusion criteria:** NR	**1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level APOE Time interval between assessments Sample weights Vit E Vit C Beta-carotene Multiple vitamin use DM HTN Smoking ETOH use Stroke Heart disease folate **Method(s) of assessing cognitive status:** NINCDS-ADRDA Other: Cognitive decline on standardized composite measure from all tests-baseline performance incorporated into composite measure **Informant interview?:**	4324/6158 completed diet info and 2 cognitive time points (authors reported was 87% of surviving members)- some excluded from group because of invalid diet data **2) Important baseline differences:** Lowest quintile of total niacin intake and niacin food intake compared to higher quintiles: higher percent of females, blacks, ind w/ stroke, and ind with low food intake of Vit E Lowest quintile of total niacin intake more likely to have APOE e4 allele Highest quintile of both total and food intake of niacin had higher prevalence of DM **3) Outcome of interest #1** Higher quintiles of total Niacin from supplements (p=0.04), from food (p=0.006), from tryptophan (p=0.03) and from niacin equivalents (p=0.01) associated with reduced risk of AD **4) Outcome of interest #2** Food intake of niacin had a linear effect on cognitive decline, but in fully adjusted model did not reach significance (p=0.12). When those with stroke or MI (p=0.002) or low cognitive scores (p=0.03) were excluded there was an sig linear association.	*For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Yes –says informant interviews for the cognitively impaired, but this differs from all other descriptions of this study		
Morris, Evans, Bienias, et al., 2003a CHAP	**Geographical location:** Chicago, IL **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 815 **Duration of follow up:** Mean 3.9 yrs **Time from risk factor assessment to final cognitive assessment:** Mean 2.3 yr	**Age:** Range: 65-94 **Sex:** [n (%)] Female: 497 (61%) Male: 318 (39%) **Race/ethnicity:** [n (%)] AA: 424 (52%) White and other: 391 (48%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged ≥65 yrs **Exclusion criteria:** NR	**Risk factor/exposure 1:** fat intake **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level APOE **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** Yes –says informant interviews for the cognitively impaired, but this differs from all other descriptions of this study	**1) Follow-up rate:** reported that 75.6% of surviving stratified sample participated (n = 842) then 815/842 had complete diet info **2) Important baseline differences:** Higher % of women and vit C users in lowest quintile of intake for both saturated and w-6 polyunsaturated fat Black more likely to be in lowest quintile of saturated fat intake and highest quintile of w-6 polyunsaturated fat intake Ind with APOE e4 mose likely to be in the lowest quintile of saturated fat intake **3) Outcome of interest #1** Saturated fat: highest quintile associated w/ increased risk of AD: RR -2.2 (1.1-4.7) Trans-unsaturated fat: Quintiles 2-5 higher risk of AD, but only quintiles 2 (2.4 ;1.1- 5.3) and 3 (2.9; 1.2-7.2) significant w-6 polyunsaturated fat: Quintile 5 had lower risk of AD (0.3; 0.1-0.8) Monounsaturated fat, total fat and	**Comments:** Question 1 Used multivariable model w/o adjustment for other dietary fat **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				dietary cholesterol not associated with AD Animal fat and vegetable fat not associated with AD in multivariable models. But when vegetable fat controlled for other dietary fat, there was a linear trend (p = 0.002) for protection against AD (although the RR for ind quintiles was not significant)	
Morris, Evans, Bienias, et al., 2002a CHAP	**Geographical location:** Chicago, Illinois **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 815 **Duration of follow up:** 3.9 yrs **Time from risk factor assessment to final cognitive assessment:** 2.3 yrs	**Age:** Mean (SD): 73.3 (9.7) **Sex:** [n (%)] Female: 505 (62) Male: 310 (38) **Race/ethnicity:** [n (%)] AA: 419 (51.4) White and other:396 (48.6) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged ≥65 yrs **Exclusion criteria:** None	**Risk factor/exposure 1:** Antioxidant-vitamin C, E, beta-carotene **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level APOE Time interval to fup **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** Yes –says informant	**1) Follow-up rate:** reported that 75.6% of surviving stratified sample participated (n = 842) then 815/842 had complete diet info **2) Important baseline differences:** For each antioxidant, ind in the upper quintiles to total intake were more likely to be white, had more education, had higherh intake of other antioxidants than ind in lower quintiles Ind with high food intake of Vit E tended to be men and to have a higher intake of fat and beta carotene, and a lower intake of Vit C Ind with high food intake of Vit C tended to be female and to have a lower intake of Vit E and total fat Ind in lowest quintile of beta-carotene intake more likely to be black and have an APOE e4 allele compared to upper quintiles	**Comments:** Question 1 In description of one sub-analysis – noted that 96 people had diet info collected within 1 yr of f/u assessment – vit E food intake result became non-significant (CI: 0.11-1.02) **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			interviews for the cognitively impaired, but this differs from all other descriptions of this study	**3) Outcome of interest #1** Vit E: Food intake only (not food and supplement): highest quintile associated with lower risk of AD (RR -0.30;0.10-0.92); trend for all quintiles p = 0.05 Food and supplements – not significant Vit C: Intake of food only – overall not sig assoc with AD. Trends do not approach significance. Quintile 4 only is associated with reduced risk of AD (RR-0.37; 0.17-0.82) Intake of food and supplements not significant Beta-carotene – neither intake of food only or food plus supplements were significantly assoc with AD **4) Outcome of interest #2** Vit E intake from food: APOE e4 negatives had reduced incidence of AD among Quintiles 3, 4, and 5 (Quintile 5 –RR-0.17; 0.06-0.47) In APOE e4 positives, Vit E not protective against AD.	9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Morris, Evans, Bienias, et al., 2003b CHAP	**Geographical location:** Chicago, Illinois **Setting:** Community **Study design:** Prospective cohort	**Age:** Range: 65-94 **Sex:** [n (%)] Female: 497(61) Male: 318 (39) **Race/ethnicity:** [n (%)] AA 505 (62)	**Risk factor/exposure 1:** fish and n-3 fatty acids, DHA, EPA, linolenic **Method of assessing risk factor/exposure 1:** Self-report	**1) Follow-up rate:** reported that 75.6% of surviving stratified sample participated (n = 842) then 815/842 had complete diet info **2) Important baseline differences:** Compared to lowest quintile of n-3 polyunsaturated fat intake, those in	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors?

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		White 310 (38)		highest quintile group were more likely to be male, to have more education, to have a hx of HTN, and to have lower consumption of Vit E and all types of fat **3) Outcome of interest #1** Compared to ind who never ate fish, those who did eat fish had lower risk of AD (RR for ≥ 2/wk fish: 0.4 (0.2-0.9). Trend p =0.07 **4) Outcome of interest #2** N-3 fatty acid: highest quintile associated with reduced risk of AD (RR=0.4;0.1-0.9); trend p = 0.01 DHA: two highest quintiles associated with reduced risk of AD (RR for highest quintile=0.03; 0.1-0.9); trend p = 0.02 EPA intake not associated with AD risk Linolenic intake not associated with AD risk	Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
	Number of participants enrolled: 815 **Duration of follow up:** 3.9 yrs **Time from risk factor assessment to final cognitive assessment:** 2.3 yrs	**Baseline cognitive status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged ≥65 yrs **Exclusion criteria:** NR	**Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level APOE Time interval to fup **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** Yes –says informant interviews for the cognitively impaired, but this differs from all other descriptions of this study		
Morris, Evans, Bienias, et al., 2005 CHAP	**Geographical location:** Chicago, Illinois **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:**	**Age:** Mean (SD):Mean range across quintiles of folate exp: 74.0-74.9 **Sex:** [n (%)] Female: Mean range of % across quintiles of folate exp: 59-68 Male: **Race/ethnicity:** [n (%)]	**Risk factor/exposure 1:** Folate and B12 **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in**	**1) Follow-up rate:** 4390/6158 completed diet info and 2 cognitive time points (authors reported was 89% of surviving members)- excluded 677 from group because of invalid diet data (does not add up to 3718) **2) Important baseline differences:** High intake total folate had more years education, higher baseline cognitive scores, greater	**Comments:** Question 2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	3718 **Duration of follow up:** 3718 ind –median 5.5 yrs 1964 ind – median 6.3 yrs **Time from risk factor assessment to final cognitive assessment:** 3718 ind -4.3 yr 1964 ind – 5.1 yr	Mean range of % across quintiles of folate exp:43-75 **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged ≥65 yrs **Exclusion criteria:** None	**analyses:** Age Race Sex Educational level Time interval between assessments Vitamin E Vitamin C Multivitamin **Method(s) of assessing cognitive status:** **Other –** Cognitive decline on standardized composite measure from all tests-baseline performance incorporated into composite measure (this was noted in previous article but not in this article) **Informant interview?:** No	consumption of vitamin E and C; less likely to have heart disease or HTN **3) Outcome of interest #1** Total intake of folate: upper to quintiles declined slightly faster than lowest quintile (p value for 5th quintile =0.002; trend p = <.001) Folate intake from food:higher quintiles generally declined slightly faster than lowest quintiles(p value for 5th quintile = 0.02; trend p = .04)	4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Morris, Evans, Bienias, et al., 2002b CHAP	**Geographical location:** Chicago, Illinois **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:**	**Age:** Mean (SD): 73.9 **Sex:** [n (%)] Female: 1791 (62) Male: 1098 (38) **Race/ethnicity:** [n (%)] AA: 1594 (55%) White: 1295 (45%) **Baseline cognitive**	**Risk factor/exposure 1:** Vitamin E and C **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in**	**1) Follow-up rate:** 4376/ 4983 completed cog screen F/U; total of 1486 excluded because no or invalid diet data, or timing of data collection inappropriate **2) Important baseline differences:** Vit E supplement users had more education and higher intake of anti-oxidant nutrients Lowest quintile of Vit E intake from food had higher ETOH use, were	**Comments:** Question 2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	2889 **Duration of follow up:** 3.2 yrs (range 1.8-5.9 yr) **Time from risk factor assessment to final cognitive assessment:** 1.8 (0.7) yrs	**status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged ≥65 yrs **Exclusion criteria:** None	**analyses:** Age Race Sex Educational level Total energy from calories Smoking ETOH use Time between assessments **Method(s) of assessing cognitive status:** Other – Cognitive decline on standardized composite measure from all tests-baseline performance incorporated into composite measure **Informant interview?:** No	more likely to be smokers. Black participants had higher intake of Vit E from food, but were less likely to use either Vit E supplements or multi-vitamins **3) Outcome of interest #1** Vitamin E total intake:highest quintile showed less decline (p=0.05) used 'multivariable alone' model Vitamin C total intake – not associated with cognitive decline **4) Outcome of interest #2** Vitamin E food intake: Highest two quintiles associated with less decline (p <0.05) Vitamin C food intake: not associated with cognitive decline	4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Morris, Evans, Bienias, et al., 2004b CHAP	**Geographical location:** Chicago, Illinois **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2560	**Age:** Mean (SD): Mean range across fat intake quintiles: 73.7-74.3 **Sex:** [n (%)] Female: mean % range across fat intake quintiles 46.4-76.0 Male: **Race/ethnicity:** [n (%)] AA: 1587 (62)	**Risk factor/exposure 1:** fat intake **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:**	**1) Follow-up rate:** 4398/4930 completed at least one cognitive follow-up; others excluded due to no diet data, invalid diet data, inappropriate timing of diet data collection, or hx of stroke or MI resulting in change of diet **2) Important baseline differences:** Ind in top quintile of both saturated and trans-unsaturated fat intake were more likely to be male, to be white, to have higher intake levels of all other	**Comments:** Question 2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Duration of follow up: Median 5.6 yr for 2560 ind Median 6.3 yr for 1397 ind **Time from risk factor assessment to final cognitive assessment:** 4.6 yr for 2560 ind	White: 973 (38) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged ≥65 yrs **Exclusion criteria:** None	Age Race Sex Educational level Total energy from calories Smoking ETOH use Time between assessments HTN Vitamin C Vitamin E **Method(s) of assessing cognitive status:** Other – Cognitive decline on standardized composite measure from all tests-baseline performance incorporated into composite measure **Informant interview?:** No	types of fat, and higher prevalence of smoking. Those with high intake of saturated fat were more likely to have higher baseline cognitive score and hx of HTN. Those with high intake of trans-unsaturated fat tended to have low consumption of alcohol. **3) Outcome of interest #1** Higher intake of saturated fat (trend p=0.04) and trans-unsaturated fat (trend p = 0.07) were linearly associated with greater decline in cognitive score over 6 yrs. When excluding individuals who changed pattern of fat intake in last 10 years and/or those scoring in lowest 15%, effect became stronger. Total fat, vegetable and animal fat, and cholesterol not associated with cognitive change	cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Morris, Evans, Schneider, et al., 2006 CHAP	**Geographical location:** Chicago, Illinois **Setting:** Community **Study design:** Prospective cohort **Number of**	**Age:** Mean (SD): range of means across folate quintiles: 71.7-73.3 **Sex:** [n (%)] Female: Male: % range across folate quintiles: 34.4-43.1	**Risk factor/exposure 1:** Vitamins B6 and B12, folate **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential**	**1) Follow-up rate:** Can't determine from info provided – combined 2 waves of incidence data **2) Important baseline differences:** High total intake of Vit B6, B12 and folate were associated with being younger, white, more education, greater participation in cognitive activities, not having an APOE e4 allele, and higher intake of Vit E and	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5%

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	participants enrolled: 1041 **Duration of follow up:** Median 3.9 yr **Time from risk factor assessment to final cognitive assessment:** 2.7 yr	**Race/ethnicity:** [n (%)] AA: % range across folate quintiles: 34.6-68.4 **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged ≥65 yrs **Exclusion criteria:** None	**confounders adjusted for in analyses:** [delete any from the list below that do not apply and add items as needed] Age Race Sex Educational level Period of observation APOE Vitamin E Niacin **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** Yes –says informant interviews for the cognitively impaired, but this differs from all other descriptions of this study	niacin. High intake of B-12 was associated with higher intake of saturated fats. **3) Outcome of interest #1** Using nutrient adjusted models comparing highest quintile to lowest quintile: Neither total folate (OR=1.6; 0.5-5.2) or folate from food (1.8; 0.8-4.1) was associated risk of AD. Neither total vitamin B-12 (0.6; 0.2-1.6) or vitamin B-12 from food (1.0; 0.3-2.7) was associated with risk of AD. Neither total vitamin B-6 (0.7; 0.2-2.4) or vitamin B-6 from food (0.7; 0.3-1.4) was associated with risk of AD.	difference? Can't Tell 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Morris, Evans, Tangney, et al., 2006a CHAP	**Geographical location:** Chicago, IL, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:**	**Age:** Mean (SD): Mean range across copper intake quintiles: 74.0-74.8 **Sex:** [n (%)] Female: Mean % range across copper intake quintiles: 57.7 - 67.1 Male:	**Risk factor/exposure 1:** Copper, zinc, iron, saturated and trans fats **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential**	**1) Follow-up rate:** Authors note 88% of survivors participated in data collection; additional subjects were excluded because of invalid dietary data **2) Important baseline differences:** Ind with high copper intake were more likely to have healthy lifestyle behaviors and higher baseline cognitive scores	**Comments:** Question 2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	3718 **Duration of follow up:** Median 5.5 yrs **Time from risk factor assessment to final cognitive assessment:** 4.3 yr	**Race/ethnicity:** [n (%)] AA: Mean % range across copper intake quintiles: 48.5-69.5 **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged >65 yrs **Exclusion criteria:** None	**confounders adjusted for in analyses:** Age Race Sex Educational level Cognitive activities Physical activities ETOH use Stroke Heart disease HTN DM Vitamin E Vitamin C Niacin Folate **Method(s) of assessing cognitive status:** Other – Cognitive decline on standardized composite measure from all tests-baseline performance incorporated into composite measure **Informant interview?:** No	**3) Outcome of interest #1** Neither total intake or food intake of copper, zinc or iron were associated with cognitive decline **4) Outcome of interest #2** Total copper intake combined with diet high in saturated and trans fat was associated with faster cognitive decline (p<0.001)	4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Morris, Evans, Tangney, et al., 2006b CHAP	**Geographical location:** Chicago, IL, USA **Setting:** Community	**Age:** Mean (SD): 73.6 Range: 65-102 **Sex:** [n (%)] Female: 2305 (62) Male: 1413 (38)	**Risk factor/exposure 1:** fruit and vegetable **Method of assessing risk factor/exposure 1:**	**1) Follow-up rate:** Authors report 92.2% fup rate at 1st fup and 89.8% fup rate at 2nd fup. Additional ind were excluded because of invalid diet data **2) Important baseline differences:**	**Comments:** Question 2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Study design: Prospective cohort **Number of participants enrolled:** 3,718 **Duration of follow up:** 3718 ind –median 5.5 yrs 1964 ind – median 6.3 yrs **Time from risk factor assessment to final cognitive assessment:** 3718 ind -4.3 yr 1964 ind – 5.1 yr	**Race/ethnicity:** [n (%)] AA: 2246 (60.4) White 1472 (39.6) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged ≥65 yrs **Exclusion criteria:** None	Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Cognitive activities Physical activities ETOH use **Method(s) of assessing cognitive status:** Other – Cognitive decline on standardized composite measure from all tests-baseline performance incorporated into composite measure **Informant interview?:** No	Ind with high intakes of fruits and vegetables were likely to be female, to be white, have more years of education, and higher physical activity level. Ind with high intake of fruit more likely to have a cardiovascular condition. **3) Outcome of interest #1** Higher intake of vegetables associated with less cognitive decline (trend p = 0.04). Higher intake of fruit not associated with rate of cognitive decline (trend p = 0.55) **4) Outcome of interest #2** High intake of green leafy vegetables showed strongest association with reduction in cognitive decline (trend p = 0.03)	2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Morris, Evans, Tangney, et al., 2005 CHAP	**Geographical location:** Chicago,IL, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:**	**Age:** Mean (SD): range across quintiles of alpha-tocopherol: 74.1-74.8 **Sex:** [n (%)] Female: % range across quintiles of alpha-tocopherol: 57.6-68 Male: % range across	**Risk factor/exposure 1:** tocopherol forms **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in**	**1) Follow-up rate:** NR in format that is useful. Combined incident cases from multiple waves of data collection. **2) Important baseline differences:** Ind with high intake of alpha-tocopherols had more education, higher intake of Vit C and n-3 fatty acid DHA. Ind with high intake of gamma tocopherol had lower intake of Vit C, higher intake of saturated	**Comments:** Question: Q1, Q2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	1041 –AD analyses 3718- cognitive decline analyses **Duration of follow up:** 1041 – median 3.9 yr 3718 – median 5.5 yr (from other study) **Time from risk factor assessment to final cognitive assessment:** 1041 - 2.7 yrs 3718 – 4.3 yr (these are estimates based on info in other papers)	quintiles of alpha-tocopherol: 32-42.4 **Race/ethnicity:** [n (%)] AA: % range across quintiles of alpha-tocopherol: 56.6-65.4 Other: % range across quintiles of alpha-tocopherol: 34.6-43.4 **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residents of three geographically contiguous neighborhoods on southside of Chicago. Aged ≥65 yrs **Exclusion criteria:** None	**analyses:** Age Race Sex Educational level APOE Cognitive activities Observation interval Saturated fat Trans unsaturated fat DHA Vitamin C **Method(s) of assessing cognitive status:** NINCDS-ADRDA Other – Cognitive decline on standardized composite measure from all tests-baseline performance incorporated into composite measure **Informant interview?:** No (Does not say used informant and based on my knowledge of methods did not use informant. But many other of their articles say used Informant for the cognitively impaired).	and trans unsaturated fats. **3) Outcome of interest #1** Lower AD risk associated with high intake of: Vit E (RR=0.74; 0.62-0.88) Gamma-tocopherol (RR=0.60; 0.41-0.88) Delta-tocopherol (RR=0.75; 0.58-0.96) Alpha-tocopherol equivalents (RR=0.56; 0.32-0.98) **4) Outcome of interest #2** Slower rate of cognitive decline associated with high intake of: Vit E (p=0.0003) Alpha tocopherol (p=0.01) Gamma-tocopherol (p=0.03) Alpha-tocopherol equivalents (p=0.005)	4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial. Food frequency questionnaire 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Morris, Scherr,	**Geographical location:**	**Age:** Mean (SD): 72.2	**Risk factor/exposure 1:**	**1) Follow-up rate:** Of those sampled 97% agreed to	**Comments:** Called non demented on basis of

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Hebert, et al., 2001 Boston EPESE	Boston, MA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 634 **Duration of follow up:** bp reported mean of 13.6 years before dx and 4.5 yrs before dx **Time from risk factor assessment to final cognitive assessment:** NR	Range: ≥ 65 **Sex:** [n (%)] Female: 402 (63.4%) Male: 232 (36.6%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 years Participating in the East Boston EPESE study Free of AD at baseline **Exclusion criteria:** NR	htn **Method of assessing risk factor/exposure 1:** Self-report Direct measurement **Risk factor/exposure 2:** antihypertensives **Method of assessing risk factor/exposure 2:** pill bottle inspection **Covariates/potential confounders adjusted for in analyses:** Age, Sex Educational level **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** No	participate 426 out of 634 (67%) had blood pressure measurements at the end of 6 years and this was the sample included in the analysis. **2) Important baseline differences:** Those with sbp ≥ 160 were older, more likely to have cv dz including htn cva, heart dz, dm **3) Outcome of interest #1** no association between sbp measured 13 yrs before dx OR 1.03 /10 mmHg (0.80 – 1.32) **4) Outcome of interest #2** inverse association between sbp measured 4 yrs before dx OR 0.82/10mmHg (0.72 – 0.95)	memory performance for many subjects. May be adequate. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? No 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Muller, Tang, Schupf, et al., 2007 WHICAP	**Geographical location:** Northern Manhattan, NY, USA **Setting:** Community	**Age:** Mean (SD): 76.1 (6.0) **Sex:** [n (%)] Female: 1234 (67.3) Male: 599 (32.7) **Race/ethnicity:** [n (%)]	**Risk factor/exposure 1:** Metabolic syndrome **Method of assessing risk factor/exposure 1:** Self-report for diabetes	**1) Follow-up rate:** 1833/2210 (denominator are those with labs done who were not demented at baseline) **2) Important baseline differences:** Those with MS were less educated, smoked more, more likely to be	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Study design: Prospective cohort **Number of participants enrolled:** 1,833 **Duration of follow up:** 4.4 (2.5) yrs **Time from risk factor assessment to final cognitive assessment:** 4.4 (2.5) yrs	Hispanic: 720 (39.3) AA: 565 (30.8) White: 548 (29.9) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Two related cohorts drawn from probability samples of Medicare recipients, aged ≥ 65 residing in Northern Manhattan. One of the two cohorts excluded individuals who self-reported prevalent dementia. Current analyses limited to subset with assessment of lipid levels. **Exclusion criteria:** NR	when insulin level not available (or use of diabetes medication) Direct measurement (for insulin, only available on 997 subjects) **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level APOE Smoking Cohort drawn from **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** No	female, more likely to be Hispanic. (Table 2 says the MS were younger and that female was not significant, but the text states differently). **3) Outcome of interest #1** Metabolic syndrome (NCEP-ATPIII criteria) was not associated with increased risk of AD (HR: 0.9; 95% CI: 0.6-1.3) n= 1833 **4) Outcome of interest #2** Metabolic syndrome (EGIRI criteria) was not associated with increased risk of AD (HR: 1.2; 95% CI: 0.6-2.5) n= 542	differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Muniz-Terrera, Matthews, Dening, et al., 2009 Cambridge City over 75s Cohort Study	**Geographical location:** Cambridge, UK **Setting:** Clinical – Primary Care Practices **Study design:** Prospective cohort	**Age:** Range: 75-84: 1719 (84%) 85+: 334 (16%) **Sex:** [n (%)] Female: 1328 (65%0 Male: 725 (35%) **Race/ethnicity:**	**Risk factor/exposure 1:** Education (left school before or after the age of 14) Profession (manual or non-manual) Married vs. not ever	**1) Follow-up rate:** 1st f/u: 1161/2053 (57%) 2nd f/u: 647/2053 (32%) 3rd f/u: 304/2053 (15%) **2) Important baseline differences:** N/A **3) Outcome of interest #1** Rate of decline of MMSE score over	**Comments:** Question 2 – no cat Dx **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? No. Selection criteria among eligible primary care patients not reported. 2) Selection minimizes baseline

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		NR	married	9 years (SE)	differences in prognostic factors? Can't Tell
	Number of participants enrolled: 2053	**Baseline cognitive status:** Non-demented	**Method of assessing risk factor/exposure 1:** Self-report	Left school prior to age 14: 0.01 (0.05)	3) Sample size calculated/5% difference? No
	Duration of follow up: Three f/u visits at 2, 7, & 9 yrs after baseline assessment	**Inclusion criteria:** Age ≥85 in 1985 and registered at one of 6 primary care practices in the Cambridge City area.	**Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Profession Marital status Baseline MMSE	Non-manual profession: 0.05 (0.06)	4) Adequate description of the cohort? No
	Time from risk factor assessment to final cognitive assessment: Average of 2, 7, & 9 yrs	**Exclusion criteria:** MMSE <24 on an in-home screening evaluation.	**Method(s) of assessing cognitive status:** MMSE as part of a detailed clinical interview.	Married: 0.01 (0.05)	5) Validated method for ascertaining exposure? Yes
			Informant interview?: No	(Note: none of the above rates of decline reached statistical significance at the p<0.05 level)	6) Validated method for ascertaining clinical outcomes? Yes
					7) Outcome assessment blind to exposure? Can't Tell
					8) Adequate follow-up period? Yes
					9) Completeness of follow-up? No (15% response rate for all 3 f/u assessments)
					10) Analysis controls for confounding? Yes
					11) Analytic methods appropriate? No (rate of decline of MMSE score over 9 years, especially given low response rate, may not be the most appropriate analysis)

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Ngandu, von Strauss, Helkala, et al., 2007 CAIDE study North Karelia Project FINMONICA study	**Geographical location:** Kuopio & Joensuu, Finland **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1449 **Duration of follow up:** Mean 21 yrs (4.9) **Time from risk factor assessment to final cognitive assessment:** Mean 21 yrs (4.9)	**Age:** Midlife evaluation: Mean (SD): 50.6 (6.0) Late-life evaluation: Mean (SD): 71.6 (4.1) **Sex:** Female: 900 (62.1%) Male: 549 (37.9%) **Race/ethnicity:** NR **Baseline cognitive status:** NR, but unlikely to be impaired at baseline in midlife **Inclusion criteria:** Participants of one of 4 separate samples (North Karelia Project and the FINMONICA study). lived in two geographically defined areas. **Exclusion criteria:** NR	**Risk factor/exposure 1:** education **Method of assessing risk factor/exposure 1:** Self-report at midlife evaluation. 3 categories: 1) low (≤5 yrs) 2) medium (6-8 yrs) 3) ≥9 yrs **Risk factor/exposure 2:** **Method of assessing risk factor/exposure 2:** **Covariates/potential confounders adjusted for in analyses:** Model 1: Age Sex F/u time Community of residence SES variables Living arrangement Midlife vascular conditions Midlife physical activity smoking APOE	**1) Follow-up rate:** 1449/2000 (72.5%) participated in the first phase of re-examination. Exclusions: 40 didn't come to 2nd evaluation, 21 had missing data on education, for a total analytical sample of 1388 of 2000 (69.4%) **2) Important baseline differences:** Those with fewer years of education were older; were more likely to have lower income, were more likely to have occupation with more physical activity, more likely to have higher blood pressure and higher cholesterol, and more likely to have higher BMI **3) Outcome of interest #1** 61 incident cases of dementia, of which 48 had AD. Total # of dementia cases increased to 117 when patient records of nonparticipants reviewed (# of additional AD cases from record reviews not reported). It appears results reported were based on the 48 AD. **4) Outcome of interest #2** Education associated with risk of dementia in a dose-dependent manner. With ≤ 5 yrs of education as the reference, crude OR (95% CI): AD:	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? No 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			late-life diseases depressive symptoms. **Method(s) of assessing cognitive status:** Screening with MMSE (screen + = MMSE scores ≤ 24) NINCDS-ADRDA DSM-IV **Informant interview?:** No	1) 6-8 yrs of education: OR=0.49 (0.24, 1.00) 2) ≥ 9 yrs: OR=0.15 (0.05, 0.40) Similar adjusted ORs. Authors conclude: none of the covariates were significant in the models, so the effect of education appears to be independent of other risk factors for dementia. **5) Outcome of interest #3—APOE** APOE did not modify the association, but the risk of dementia and AD was very low among APOE noncarriers with high education.	
Nickelson, Lufkin, Riggs, et al., 1998	**Geographical location:** Rochester, MN & Scottsdale, AZ **Setting:** Clinical – Mayo Clinics **Study design:** RCT **Test intervention:** raloxifene 60 mg or 120 mg **Comparator intervention(s):** placebo **Number of participants enrolled:** 143	**Age:** Mean (SD): 68.4 Range: 51-76 **Sex:** [n (%)] Female: 143 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Not stated, but baseline testing indicates good fct **Inclusion criteria:** Good health except for osteoporosis, free of any serious acute or chronic medical	**Risk factor/exposure 1:** Raloxifene 60 or 120mg vs placebo **Method of assessing risk factor/exposure 1:** clinical trial pill count **Covariates/potential confounders adjusted for in analyses:** Age Baseline cognitive status **Method(s) of assessing cognitive status:** [Other –	**1) Follow-up rate:** 143 randomized 48 placebo; 48 rlx 60mg and 48 rlx 120mg Followup rate Pl 93.7 vs RLX 60mg 95.8 vs RLX 120mg 93.6 **2) Important baseline differences:** Mean age was slightly older in the Rlx 60 mg group p 0.028. alcohol consumption 3 drinks/wk was greater in the placebo than 60 or 120 mg rlx (33 vs 15 vs 20%) p .022 **3) Outcome of interest #1** Memory assessment clinics battery Walter Reed performance assessment battery At 12 months there were no differences in the MAC or PAB	**Comments:** Among 10 cognitive measures there were no differences in any measures at 12 months. **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Partial. Last Observation Carried Forward is suboptimal approach. 6) Differential dropout rate < 10%: No 7) Overall dropout rate < 30%: No 8) Conflict of interest reported and insignificant? Can't Tell 9) Randomization adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Duration of follow up: 12 months **Time from risk factor assessment to final cognitive assessment:** 12 months	condition that might affect bone or calcium metabolism, and fully ambulatory. Postmenopausal status confirmed by serum estradiol ≤ 73 pmol/l and follicle stimulating hormone ≥ 30 IU/l in age < 60. Osteoporosis documented by Dx of at least one non-traumatic vertebral fracture and a bone mineral density of the lumbar spine or proximal femur of less than the tenth percentile of normal postmenopausal women. **Exclusion criteria:** Pts with bone disorders other than osteoporosis, clinically significant menopausal symptoms (hot flashes, sweating, etc.), any history of cancer (except superficial basal or squamous cell carcinoma of the skin) within the previous 5 years, acute or chronic liver disease, history of deep vein thrombosis or cerebral vascular accident, or impaired kidney function were excluded. Also, Tx	Memory assessment clinics battery Walter Reed performance assessment battery **Informant interview?:** No		10) Allocation concealment adequate? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		with estrogen, progestin, calcitonin, androgen, or systemic corticosteroid more recently than 6 months prior to study were grounds for exclusion.			
Niti, Yap, Kua, et al., 2009 **AND** **Ng, Niti, Zaw, et al., 2009** Singapore Longitudinal Aging Study (SLAS)	**Geographical location:** Southeast region of Singapore **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2808 eligible @ baseline (of which 2611 were eligible for f/u) 1487 analyzed **Duration of follow up:** Mean 1.46 (0.5) **Time from risk factor assessment to final cognitive assessment:** Mean 1.5 years	**Age:** Mean (SD): 65.4 (7.0) **Sex:** [n (%)] Female: 944 (63.5%) Male: 543 (36.5%) **Race/ethnicity:** [n (%)] Chinese 1487 (100%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Chinese participants in the SLAS cohort. **Exclusion criteria:** Baseline MMSE score ≤23.	**Risk factor/exposure 1:** Depressive symptoms. **Method of assessing risk factor/exposure 1:** Local Chinese version of the 15-item Geriatric Depression Scale (GDS). "Depressed symptoms" defined as GDS ≥15. **Risk factor/exposure 2:** APOE genotype **Method of assessing risk factor/exposure 2:** Polymerase chain reaction (PCR) **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline MMSE	**1) Follow-up rate:** 1487 of 2611 (57%). 15 unfit to be interviewed, 444 refused, 426 could not be contacted, 53 died. Of the remaining 1673 who completed f/u interviews, 169 were excluded because of cognitive impairment at baseline and 17 excluded because of missing APOE genotype data. **2) Important baseline differences:** N/A **3) Outcome of interest #1** Incident cognitive impairment: Overall: n=44/1487 (3.0%) Not depressed: n=35/1329 (2.6%) Depressed: n=9/158 (5.7%) Adjusted odds ratio: 2.29 (95% CI: 1.05, 5.00; p=0.04) **4) Outcome of interest #2** Incident cognitive decline, Adjusted OR (95% CI): GDS ≥5: 0.95 (0.61,1.48) APOE carrier: 1.10 (0.86,1.41) Interaction, GDS ≥5 x APOE status: APOE noncarriers: 0.73 (0.44, 1.21)	**Comments:** Question 2 – no cat Dx Same study sample used for both articles. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Partial (57%) 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			APOE genotype Length of f/u Vascular risk factors or events **Method(s) of assessing cognitive status:** MMSE "Cognitive decline" defined as ≥1 point drop in MMSE score from baseline to f/u. **Informant interview?:** No	APOE carriers: 2.89 (1.03, 8.12)	
Niti, Yap, Kua, et al., 2008 Singapore Longitudinal Aging Study cohort	**Geographical location:** South East region of Singapore **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2611 **Duration of follow up:** 1-2 years. Median= 1.5 years **Time from risk factor assessment to final cognitive**	**Age:** Mean (SD): 66.0 (7.3) **Sex:** [n (%)] Female: 1063 (65%) Male: 572 (35%) **Race/ethnicity:** [n (%)] Chinese **Baseline cognitive status:** NR, but analyses were re-run excluding those with MMSE <24 and reportedly results were the same **Inclusion criteria:** Residents of South East Singapore who consented to	**Risk factor/exposure 1:** Physical, social and productive activity **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status APOE Functional status Number of co	**1) Follow-up rate:** Of 2611, 45 died before follow up. Of the 2566, 1635 were included in analysis – 63.71% **2) Important baseline differences:** Thos who were lost to follow up were more likely to be men, have lower MMSE scores and lower scores on physical, social as well as productive activity. After categorizing baseline level of leisure activities into tertiles, the trend statistic was significant for those with fewer leisure activities to older, have lower MMSE score, less likely to be female, more likely to have ≤ 6 yrs education, have more comorbid conditions, have more vascular risk factors/events, more likely to be depressed, and more likely to currently smoke.	**Comments:** Question 2 – no cat Dx **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes (Response to the survey based methods was more than 75%) 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment: 1-2 years. Median= 1.5 years	participate in study >55 yrs of age **Exclusion criteria:** NR	morbidities Vascular risk factor/events Depression Smoking Alcohol **Method(s) of assessing cognitive status:** Other – Longitudinal cognitive change on MMSE **Informant interview?:** No	**3) Outcome of interest #1** Compared to those who had low leisure activity levels the odds of cognitive decline among those with high levels of leisure activity was OR = 0.62 (0.46-0.84) and those who had medium leisure activity was OR = 0.60 (0.45 – 0.79) **4) Outcome of interest #2** Among those who had MMSE ≥ 24, Compared to those who had low leisure activity levels the odds of cognitive decline for those with high levels of leisure activity was OR = 0.62 (0.46-0.85) and those who had medium leisure activity was OR = 0.61(0.46 – 0.72) **5) Outcome of interest #3** Compared to those who did not engage in any productive activity, those who engaged in at least one productive activity had lower cognitive decline OR = 0.36 (0.20- 0.65) In the total sample, participation in at least one social or physical activity was not associated with dementia. However, in the APOE carriers, those who participated in at least one physical activity (OR=0.34; 95% CI: 0.17-0.68) or at least one social activity (OR=0.40; CI: 0.16-0.99) were less likely to become demented.	exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? No 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Okereke, Kang, Cook, et al., 2008 Physician's Health Study and Women's Health Study	**Geographical location:** Throughout the US **Setting:** Community **Study design:** RCTs – this is secondary analyses in two separate RCTs. The one RCT was to examine prevention of CVD, cancer and age-related eye disease with vitamin supplements. The other RCT was to examine prevention of CVD and cancer using vitamin E. **Number of participants enrolled:** PHSII- 5209 WHS-5199 **Duration of follow up:** PHSII-mean 2 yrs WHS- mean 4 yrs **Time from risk factor assessment to final cognitive assessment:** PHSII-mean 2 yrs WHS- mean 4 yrs	**Age:** Mean (SD): PHSII: DM = 74.3, No DM = 74.1 (total cross-sectional sample) WHS: DM=71.5, No DM=71.9 (total cross-sectional sample) **Sex:** [n (%)] Male and female samples from different source studies, so they were analyzed separately. Percentage of each does not seem relevant here. **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented (ind were included as long as they were able to complete the telephone cognitive measures, so may have included some demented) **Inclusion criteria:** Participants in the PHSII or WHS and ≥ 65 yr old **Exclusion criteria:** Ind with onset of DM prior to age 25	**Risk factor/exposure 1:** Diabetes **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Educational level Baseline cognitive status BMI HTN Cholesterol Smoking ETOH use HRT Physical activity Depression history Observation time **Method(s) of assessing cognitive status:** Other – difference in standardized test scores from baseline to fup **Informant interview?:** No	**1) Follow-up rate:** PHSII-5209/5907; WHS – 5199/6326 **2) Important baseline differences:** Men and women with DM were more likely to have HTN, high cholesterol, be overweight or obese, more sedentary, have low ETOH consumption, and lower baseline cognitive scores. Women with DM were less likely to take HRT. **3) Outcome of interest #1** Men with DM showed greater cognitive decline than men w/o diabetes on the TICS (-0.37; -0.64--.09), global cognitive score (-0.07; -0.13-0.00, ns) and verbal memory (-0.07 (-.014 to 0.01, ns) **4) Outcome of interest #2** Women with DM showed greater cognitive decline than women w/o diabetes on the TICS (-0.47; -0.71to -0.22), global cognitive score (-0.09; -0.15 to -0.04) and verbal memory (-0.09 (-.015 to -0.02) **5) Outcome of interest #3** There was a dose response effect with duration of diabetes for both men and women for the TICS and global memory score and for the verbal memory score in men	**Comments:** Question 2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Packard, Westendorp, Stott, et al., 2007 PROSPER study	**Geographical location:** Scotland, Ireland, The Netherlands **Setting:** Clinical – Primary care **Study design:** Observational analysis from an RCT **Test intervention:** Pravastatin **Comparator intervention(s):** Placebo **Number of participants enrolled:** 5804 **Duration of follow up:** Mean = 3.2 years (range 0.7 to 4.2) **Time from risk factor assessment to final cognitive assessment:** Mean = 3.2 years	**Age:** Mean (SD): 75 Range: 70-82 **Sex:** [n (%)] Female: 3000 (52%) Male: 2804 (48%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age 70-82 High risk for (≈50%) or known vascular disease (≈50%) Total cholesterol 154 to 347 mg/dl and triglyceride < 231 mg/dl Adhere to study drug of >=75% and <=120% during run-in phase **Exclusion criteria:** MMSE < 24 Various medical criteria related to safety Alcohol or drug abuse Current lipid-lowering treatment	**Risk factor 1:** LDL-C; HDL-C **Method of assessing risk factor 1**: Directly measured twice at baseline in a central laboratory standardized through CDC **Covariates/potential confounders adjusted for in analyses:** Age, sex, country, education; history of vascular disease, MI, stroke, TIA, smoking, antihypertensive medication, BP, BMI, DM; triglyceride, treatment allocation, apoe e4,and baseline cognitive test scores **Method(s) of assessing cognitive status:** Other – MMSE, picture-word learning test, Stroop color word test, letter digit coding test **Informant interview?:** No	**Follow-up:** 86% of potential visits completed; **Treatment adherence:** 94% in intervention and control **Cognitive decline:** Differences between last on-treatment and the second of two baseline measures. Difference in changes scores reported (by LDL-C and HDL-C tertile) No significant difference for any cognitive measure: MMSE, Letter digit codes, Picture word learning test-immediate and delayed recall, Stroop test Activities of daily living and Independent activities of daily living: No significant difference by LDL-C or HDL-C tertile for either outcome **Continuous outcome** [see instructions above]	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial; race not given 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Panza, D'Introno, Colacicco, et al., 2008 Italian longitudinal study on aging	**Geographical location:** Italy – 8 cities **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 5632 overall, 2963 in this analytic sample but only 1524 included for incident MCI **Duration of follow up:** 3.5 years **Time from risk factor assessment to final cognitive assessment:** 3.5 years	**Age:** Mean (SD): 71.9 (5.0) **Sex:** [n (%)] Female: 663 (43.5%) Male: 861 (56.5%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age 65-84 Randomly selected Completed baseline neuropsychological testing **Exclusion criteria:** Dementia	**Risk factor/exposure 1:** Depression **Method of assessing risk factor/exposure 1:** Direct measurement – geriatric depression scale (GDS) ≥ 10 at baseline **Risk factor/exposure 2:** Vascular risk factors: coronary artery disease, HTN, diabetes mellitus, stroke **Method of assessing risk factor/exposure 2:** Self-report Direct measurement (examination and blood values, EKG) Medical record **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Stroke, HTN, DM, smoking, total cholesterol **Method(s) of assessing cognitive**	**1) Follow-up rate:** Unclear **2) Important baseline differences:** NR **3) Outcome of interest #1** 113 incident cases of MCI. RR for MCI with depressive symptoms (1.25; 0.85-1.84) **4) Outcome of interest #2** Subgroup analysis showed increased risk for MCI among those with depressive symptoms and without CAD, RR 1.5 (1.0-2.3); among those with CAD, RR 0.5 (0.2-1.3). However, this association was no longer significant after adjusting for age, gender, education, stroke, HTN, smoking, DM and total cholesterol.	**Comments:** Question 2 – yes cat Dx 65% power to detect a RR of 1.25 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial, subset with complete data 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Yes 4) Adequate description of the cohort? Partial, race not given 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			status: 2-stage assessment using modified Petersen's criteria (subjective memory complaint not required and allowed for non-cognitive disabilities) **Informant interview?:** uncertain		
Paterniti, Verdier-Taillefer, Dufouil, et al., 2002 EVA Study	**Geographical location:** Nantes, France **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1189 (1003 analyzed) **Duration of follow up:** 4 years **Time from risk factor assessment to final cognitive assessment:** 2-4 years	**Age:** Range: 59- 71 years **Sex:** Female: 429 (42.8%) Male: 574 (57.2%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented Mmse>25 **Inclusion criteria:** 59-71 years old **Exclusion criteria:** MMSE<26	**Risk factor/exposure 1:** Depression (CESD>16 for men; >22 for women) Episodic depression = above threshold at one timepoint Persistent depression = above threshold at >1 timepoint **Method of assessing risk factor/exposure 1:** Self-report at baseline, 2- and 4-year follow-up **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Alcohol use Tobacco use	**1) Follow-up rate:** 1003/1189 = 84% **2) Important baseline differences:** More smokers in depressed group **3) Outcome of interest #1** MMSE decline >=3 points at 4 year f/u (161 cases) CESD> threshold: OR=1.55 (95% CI 0.95 to 2.55) Not depressed = referent Episodic depression: OR=1.22 (95% CI 0.68 to 2.18) Persistent depression: OR=2.10 (95% CI 1.23 to 3.58) **4) Outcome of interest #2** Low cognitive functioning (MMSE< 26 at 2- and 4-year f/u. CESD > threshold: OR=3.22 (95% CI, 1.23 to 8.42) **5) Outcome of interest #3** Change in MMSE (4 year - baseline) CESD below threshold (n-881): Mean change=-0.88 (SE 0.06) CESD above threshold (n=122):	**Comments:** More subjects with depression at baseline did not complete follow-up **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Partial 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the cohort: Yes 5) Validated method for ascertaining exposure: Yes 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Yes 9) Completeness of follow-up: Yes. 10) Analysis controls for confounding: Yes 11) Analytic methods appropriate: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Psychotropic drug use Six chronic medical conditions Baseline MMSE (outcome #3 only) **Method(s) of assessing cognitive status:** Other – Cognitive decline= Decline in MMSE >=3 points; Low cognitive function = MMSE <25 at 2- and 4-year follow-up **Informant interview?:** No	Mean change = -1.42 (SE 0.16)	
Peila, White, Masaki, et al., 2006 Honolulu-Heart Program	**Geographical location:** Oahu, HI **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3734 in HHP cohort; 1294 in this analysis **Duration of follow up:** midlife bps from 1965-74, latelife bp from 1991-3 Cognitive baseline 1991 follow up 1994	**Age:** Mean (SD): Hypertensive 77 (0.1) Normotensive 76.3 (0.2) **Sex:** [n (%)] Female: 0 (0%) Male: 1294 (100%) **Race/ethnicity:** [n (%)] Japanese-American 1294 (100%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Japanese-American men; born between	**Risk factor/exposure 1:** antihypertensives **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2:** htn **Method of assessing risk factor/exposure 2:** Direct measurement or self-report of HTN or selsf report of antihypertensive medication	**1) Follow-up rate:** analysis of 1294 who were normotensive t/o study or hypertensive t/o study. Looks like 1223 had abnl bp or missing bp, 64 had tx early but not late and 10 had missing tx data Adjusted loss to f/u: 66.8% in treated vs. 57.4% in untreated hypertensives 31% seem to have been deaths, refusals, demented but I don't see a breakdown **2) Important baseline differences:** subj with htn were older, had higher bp's at mid and late life, higher bmi, lower abi, more vasc dz, more apoE4 **3) Outcome of interest #1** **Incident dementia = 108 (AD – 65;**	**Comments:** Question 1 for antihypertensives **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Partial 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Time from risk factor assessment to final cognitive assessment: Variable: 4 to >12 years	1900 – 1919; living in Oahu, HI Specific criteria for this study sample not well specified **Exclusion criteria:** Subjects with missing data on BP Hypertensive treated at mid-life but not late-life Missing data on duration of anti-HTN treatment	**Covariates/potential confounders adjusted for in analyses:** Age, midlife bmi, smoking, cad, cva, atherosclerosis (using abi), apoE4, education **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM-IIR/IV In those screening positive on Cognitive Abilities Screening Instrument **Informant interview?:** yes for those who were evaluated by screen positive men	**AD/VaD – 19)** duration of tx, hr for ad 0-5 yrs 0.62(0.27-1.43) 5-12 yrs 0.54 (0.21-1.36) >12 yrs 0.35 (0.16-0.78) as comopared to never treated hypertensives Untreated normotensives 0.26 (0.10-0.66) **4) Outcome of interest #2** tx > 12 yrs as compared with normotensives 0.82 (0.28-2.38) not specifically ad **5) Outcome of interest #3:** Annual decline in CASI score was greater for never treated hypertensives (-1.46) compared to treatment for 5-12 years (-1.14) and normotensives (-1.01) but was not statistically significant compared to 0-5 years treatment (-1.22) or >12 years treatment (-1.08)	8) Adequate follow-up period? Yes 9) Completeness of follow-up? No 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Petersen, Thomas, Grundman , et al., 2005	**Geographical location:** multiple sites throughout the US and Canada **Setting:** Clinical – 69 ADCS in US and Canada **Study design:** RCT **Test intervention:**	**Age:** Mean (SD): 72.9 (7.3) **Sex:** [n (%)] Female: 352 (46) Male: 417 (54) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** MCI (amnestic)	**Risk factor/exposure 1:** Vitamin E **Method of assessing risk factor/exposure 1:** Self report – but RCT so some objective evidence **Covariates/potential confounders adjusted for in**	**1) Follow-up rate:** 230 of 769 discontinued during trial – no sig diff between treatment arms **2) Important baseline differences:** No significant differences **3) Outcome of interest #1** No difference in rate of progression to AD between vitamin E and placebo groups at any point, either among all patients or among apolipoprotein e4 carriers. (HR =1.02; 95% CI, 0.74 to 1.41; P=0.91).	**Comments:** None **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	2000 IU of vitamin E and multivitamin daily; OR 10 mg of donepezil, and a multivitamin OR a multivitamin daily. **Comparator intervention(s):** Other arms (donepezil and multi-vit OR multi-vit) **Number of participants enrolled:** 769 **Duration of follow up:** 3 years **Time from risk factor assessment to final cognitive assessment:** 3 years	**Inclusion criteria:** Had amnestic MCI, impaired memory, a Logical Memory delayed-recall score approximately 1.5 to 2 SD below an education-adjusted norm, a CDR of 0.5, a score of 24 to 30 on MMSE, and between 55 to 90 years old. **Exclusion criteria:** NR	**analyses:** Age Baseline cognitive status APOE **Method(s) of assessing cognitive status:** NINCDS-ADRDA Other – Change on cognitive measures, CDR, Activities of Daily Living Scale; the Global Deterioration Scale **Informant interview?:** Yes	At 36 months, no differences in secondary outcomes between vitamin E and placebo groups	7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes
Plassman, Havlik, Steffens, et al., 2000 *(WWII Veterans with head injury)*	**Geographical location:** All over US **Setting:** Other –World War II veterans **Study design:** Retrospective cohort **Number of participants enrolled:** 2361	**Age:** Mean (SD): 73.05 in the exposed and 72.78 in the unexposed **Sex:** [n (%)] Female: 0 (0%) Male: 2361 (100%) **Race/ethnicity:** [n (%)] 95% Caucasian 3.5 % AA 1.5 % Other races	**Risk factor/exposure 1:** Head injury **Method of assessing risk factor/exposure 1:** Self-report Medical record **Risk factor/exposure 2:** APOE	**1) Follow-up rate:** Of the 5444 identified to be eligible, 2361 (43.36%) completed the baseline interview. Of this sample, 1776 (75.22%) were included in the analysis. The others were excluded due to medical reasons and other exclusion criteria. **2) Important baseline differences:** Among those exposed to head injury, those who agreed to participate had higher cognitive functioning and were more educated than those who	**Comments:** Objective evidence of head injury gathered from hospital records and long period of follow up make this an important study. Though this was not a community sample, it is not feasible to recruit a sample for TBI in for cohort study from the community. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial. Retrospective design may lead to bias.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Duration of follow up: Approximately 55 years **Time from risk factor assessment to final cognitive assessment:** Approximately 55 years.	**Baseline cognitive status:** No marked cognitive sequelae for 3 months after head trauma. **Inclusion criteria:** World War II US Navy or Marine male veterans during 1944 to 1945 who had a head injury that was 1) was documented in the military medical records, 2) occurred during military service, 3) produced loss of consciousness, post-traumatic amnesia, or skull fracture, 4) did not penetrate the dura mater, and 5) did not result in marked cognitive impairment or neurologic sequelae more than 3 months post-trauma. **Exclusion criteria:** 1) the medical record lacked evidence of head injury, loss of consciousness, posttraumatic amnesia, or hospitalization for head trauma; 2) the only reported head injury was before enlistment; 3) the record documented a	**Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Educational level APOE **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes	refused to participate. **3) Outcome of interest #1** History of head injury increased the risk of AD (hazard ratio [HR] = 2.00, 95% CI = 1.03 to 3.90) After controlling for age, HR remained the same for AD (HR = 2.01, 95%CI = 1.03 to 3.91) **4) Outcome of interest #2** Risk for AD increased with severity of head injury Compared with the group with no head injury, there was increased risk of AD for Moderate head injury: (HR = 2.32,95% CI = 1.04 to 5.17) Severe head injury : (HR = 4.51, 95% CI = 1.77 to 11.47) but not for mild head injury (HR = 0.76, 95% CI = 0.18 to 3.29) **5) Outcome of interest #3** After controlling for head injury and years of education, the HR for AD associated with homozygous e4 was 13.97 (95% CI = 4.64 to 42.01) and for e4 heterozygotes was 1.03 (95% CI = 0.43 to 2.50) when compared with men with no e4 as a reference group	2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes. 8) Adequate follow-up period? Yes 9) Completeness of follow-up? No 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		penetrating head injury, depressed skull fracture, brain surgery, or severe neurologic sequelae; 4) the individual was female or not in the armed services during 1944 to 1945; 5) the individual died during military service .			
Podewils, Guallar, Kuller, et al. 2005 Cardiovascular Health Cognition Study (CHCS – sub-group of CHS)	**Geographical location:** Sacramento Co., CA; Washington Co., MD; Forsyth Co., NC; Pittsburgh, PA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3375 **Duration of follow up:** 5.4 yrs **Time from risk factor assessment to final cognitive assessment:** 5.4 yrs	**Age:** Mean (SD): 74.8 (4.9) **Sex:** Female: 59.1% Male: 40.9% **Race/ethnicity:** Caucasian: 85% Non-Caucasian: 15% **Baseline cognitive status:** Non-demented **Inclusion criteria:** Residing in areas listed above Age ≥ 65 years Participated in the Cardiovascular Health Cognition Study in 1992-2000 **Exclusion criteria:** Dementia at baseline	**Risk factor/exposure 1:** Leisure-time energy expenditure and an activity index reflecting # of different physical activities was calculated." **Method of assessing risk factor/exposure 1:** Self-report Proxy report Direct measurement Medical record **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status apolipoprotein E	**1) Follow-up rate:** 3608 included in this study. Outcomes available for 3375. 93%follow up rate. N=3041 for fully adjusted models **2) Important baseline differences:** Compared with nonparticipants, CHCS participants were younger, more educated, and less likely to have cardiovascular disease **3) Outcome of interest #1--AD** Table 5. Multivariate Hazards Ratio (95% CI) 1) 0-1 activities: 1.0 (referent) 2) 2 activities: 0.73 (0.49, 1.08) 3) 3 activities: 0.85 (0.57, 1.29) 4) ≥4 activities: 0.44 (0.34, 0.88) p-trend 0.03 **4) Outcome of interest #2** "We identified an inverse association between physical activity and	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			genotype (APOE) (e4 or non-e4), magnetic resonance imaging white-matter-grade score (<3 or _3), activities of daily living impairment (<1 or _1), instrumental activities of daily living impairment (<1 or _1), Lubben Social Network Score , and social support score **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM ICD **Informant interview?:** No	dementia (and AD) for APOE noncarriers, but found no association for APOE carriers."	
Posner, Tang, Luchsinger, et al., 2002 Washington Heights-Inwood Columbia Aging Project (WHICAP)	**Geographical location:** Northern Manhattan, NY **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1259	**Age:** Mean (SD): Incident AD 79.3 (6.7 Incident VaD 77.9 (6.2) Free of dementia 75.0 (5.6) **Sex:** [n (%)] Female: Incident AD 108 (12.4%) Incident VaD 41 (4.7%) Dementia-free 721	**Risk factor/exposure 1:** htn **Method of assessing risk factor/exposure 1:** Self-report and Direct measurement measured x 3 with dinamap, last reading used, >140 sbp and > 90 dbp considered htn, not clear how self report counted.	**1) Follow-up rate:** 540/1799 (30%) died, refused, or moved; those w/ f/u were younger, more likely to be Hispanic, and less likely to have DM or heart disease **2) Important baseline differences:** subj with htn had more heart dz, dm and cva and less smoking **3) Outcome of interest #1** Incident AD=157; Incident VaD=56; risk of AD with a history of htn: HR= 0.8 (95% CI, 0.6-1.1)	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Partial 4) Adequate description of the cohort? Yes 5) Validated method for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Duration of follow up: every 18 mos up to seven years for cog testing **Time from risk factor assessment to final cognitive assessment:** Variable, up to 7 years.	(83.1%) Male: Incident AD 49 (12.5%) Incident VaD 15 (3.8%) Dementia-free 322 (82.4%) **Race/ethnicity:** [n (%)] African-American Incident AD 62 (15.2%) Incident VaD 22 (5.4%) Dementia-free 328 (80.4%) Hispanic Incident AD 71 (12.7%) Incident VaD 25 (4.5%) Dementia-free 458 (81.8%) White Incident AD 23 (8.2%) Incident VaD 9 (3.2%) Dementia-free 249 (88.3%) Other Incident AD 1 (11.1%) Incident VaD 0 (0%) Dementia-free 8 (88.9%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participant in	**Covariates/potential confounders adjusted for in analyses:** Age Race, Sex, Educational level, dm, heart disease (mi, chf, angina) **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** No	**4) Outcome of interest #2** Treatment of htn did not affect risk estimates for AD: no tx HR= 0.96 (95% CI 0.6 – 1.5), tx HR 0.86 (95% Ci 0.6 – 1.5) In additional analyses, no additive or synergistic effects were found between HTN and other vascular risk factors and risk of AD. **5) Outcome of interest #3** GEE analysis of composite factors for memory, language, cognition (based on neuropsych testing) showed no association between HTN and cognitive peformance.	ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Partial 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		Washington Heights-Inwood Columbia Aging Project; randomly selected; agreed to participate (1259/2126), no AD @ baseline; Medicare recipient; ≥ 65 yo **Exclusion criteria:** NR			
Potter, Plassman, Helms, et al., 2006 Duke Twins Study	**Geographical location:** throughout the US **Setting:** Community Other – Twin Registry **Study design:** Prospective cohort **Number of participants enrolled:** 3880 **Duration of follow up:** 7 years **Time from risk factor assessment to final cognitive assessment:** 7 years	**Age:** Mean (SD): 65.83 (2.74) **Sex:** [n (%)] Female: 0% Male: 100% **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Member of the NAS-NRC Twin Registry of male WWII veterans. Not demented. Both members of twin pair have occupation data and cognitive data. **Exclusion criteria:** NR	**Covariates/potential confounders adjusted for in analyses:** Age Educational level Baseline cognitive status Twin pairing Medical conditions **Method(s) of assessing cognitive status:** Other – Cognitive decline on TICS-m **Informant interview?:** No –not for this part of the study	**1) Follow-up rate:** NR **2) Important baseline differences:** NR **3) Outcome of interest #1** Within twin pairs, jobs with higher general intellectual demands were associated with more improvement in cognitive function from baseline to follow-up (p = 0.011) Within twin pairs, jobs with higher physical exertion (p = 0.002) and higher visual attention (p = 0.023) was associated with greater cognitive decline. **4) Outcome of interest #2** Within twin pairs, these occupational factors contributed little to cognitive change compared to the baseline cognitive score, the twin pairing, and education.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? No, not blind to occupation but would not have known occupational factors 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
					11) Analytic methods appropriate? Yes
Price, Stewart, Deary, et al., 2008 Aspirin for Asymptomatic Atherosclerosis (AAA) Study	**Geographical location:** Edinburgh, Glasgow, & Lanarkshire, in Central Scotland **Setting:** Clinical – mailing to general medical practices **Study design:** RCT **Test intervention** Daily enteric aspirin 100mg **Comparator intervention(s)** placebo **Number of participants enrolled:** 3350 randomized 504 enrolled after cognitive testing 399 in subset at 5 yr f/u **Duration of follow up:** 5 years **Time from risk factor assessment to final cognitive assessment:** Final cognitive	**Age:** (at randomization) Mean (SD): 62 (7) Range: 50 - 75 **Sex:** [n (%)] Female: 2396 (71.6%) Male: 954 (28.4%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Normal **Inclusion criteria:** > 50 yo; participating in Aspirin for Asymptomatic Atherosclerosis Trial **Exclusion criteria:** History of MI, angina, PAD, or stroke; if taking aspirin or warfarin; ankle brachial index >0.95 in both legs; severe indigestion; chronic liver or kidney disease; chemotherapy; contraindications to Tx w/ aspirin; an abnormally high or low packed cell volume	**Risk factor/exposure 1:** RCT asa (100 mg daily) /placebo given **Covariates/potential confounders adjusted for in analyses:** Age Sex, abi, cholesterol, smoking, Carstairs deprivation category, baseline test results **Method(s) of assessing cognitive status:** Other – Change in cognitive score over time **Informant interview?:** No	**1) Follow-up rate:** 24.8% of ASA lost, 16.8% of placebo lost **2) Important baseline differences:** We don't have good info on cognitive change subset. **3) Outcome of interest #1** No significant differences in the change in cognitive ability over the five years for any of the individual tests or for the general factor between the treatment groups.	**Comments:** Can only use the cognitive change subgroup (N=399). **Quality assessment:** *For RCTs:* 1) Baseline comparability? Can't Tell 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? Partial 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment about 5 yrs post enrollment in RCT				
Prince, Cullen, and Mann, 1994 MRC study	**Geographical location:** 226 general practices in UK **Setting:** Community (drawn from general practice lists) **Study design:** Nested case-control **Test intervention:** Atenolol 50mg daily (n=640) or hctz 25mg + amiloride 2.5mg daily (n=633) adjusted to BP target range **Comparator intervention(s):** Placebo (n=1311) **Number of participants enrolled:** 2651 in cognitive substudy; 453 included in this analysis **Duration of follow up:** 54 months (4.5 years) **Time from risk factor assessment to final cognitive**	**Age:** Range: 65 – 74 years **Sex:** NR **Race/ethnicity:** NR **Baseline cognitive status:** [delete all that do not apply] Non-demented, but only routine clinical assessment **Inclusion criteria:** SBP 160-209 and mean DBP < 115 mmg Hg Age 65-74 **Exclusion criteria:** Taking anti-HTN med CHF, angina, DM, asthma or other serious disease MI or CVA w/in 3 months	**Risk factor/exposure 1:** Area of residence from birth to 15 years (rural/urban) 2. Maternal age>34; paternal age >37 3. Paternal social class 4. Education <10 years 5. Current smoking 6. Elevated depression score **Method of assessing risk factor/exposure 1:** Self-report + Proxy report **Risk factor/exposure 2:** Cholesterol >7.2mmol 2. BMI 3. SBP >190 at baseline 4. IQ (NART score) **Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential**	**1) Follow-up rate:** 73% during trial; only 67% of the PALT decliners completed further cognitive evaluation **2) Important baseline differences:** NR **3) Outcome of interest #1** 223 PALT decliners; Within PALT decliners, Incident dementia = 50 (AD=31); AD Current rural residence OR 0.28 (0.08-0.94) Smoking >=10 cigarettes daily: OR 4.38 (1.47-13.1) Dementia: Adjusted OR showed no significant association for: area of residence from birth to age 15, season of birth, paternal social class, serum cholesterol BMI, systolic HTN, smoking, ecg arrythmia, extreme fall in SBP or DBP **4) Outcome of interest #2** Risk factors for cognitive decline on the PALT Moduretic Rx: OR 2.00 (95% CI 1.17-3.45) Low premobid IQ: OR=2.03 (1.27-3.26) <10 years education: 2.12 (1.20-3.57); no secondary school OR 2.20 (1.25-3.88); no tertiary education OR	**Comments:** Multiple comparisons – no adjustment Limited power (post-hoc calculations estimate 37-50%) Baseline IQ higher than general population Only 63% of controls were available for additional information on exposures **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Partial 3) Sample size calculated/5% difference? Yes, Post-hoc 4) Adequate description of the cohort? No 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Not Applicable 10) Analysis controls for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment: 4.5 years		**confounders adjusted for in analyses:** Age Sex IQ FH of dementia Area of residence **Method(s) of assessing cognitive status:** 2-stage screening - NINCDS-ADRDA DSM-IIIR Other – Paired associated learning test (PALT) decliner = >=16 at baseline and <16 at f/u **Informant interview?:** Yes- for a small subset	2.02 (1.00-4.08) Advanced paternal age: OR 0.49 (0.27-0.91)	confounding? Can't Tell 11) Analytic methods appropriate? Yes
Prince, Rabe-Hesketh, and Brennan, 1998 MRC Treatment Trial of Hypertension in Older Adults	**Geographical location:** United Kingdom **Setting:** Clinical – UK general practices **Study design:** Nested case-control analysis in sample recruited for RCT of anti-hypertensive medication treatment **Number of participants enrolled:**	**Age:** Mean (SD): 70 years Range: 65 – 74 years **Sex:** Female: 58% Male: 42% **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** these are trial participants so theoretically could give	**Risk factor/exposure 1:** nsaids **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Entry PALT score, entry depression score, NART score	**1) Follow-up rate:** 62% had four data pts, 88% had 3 data pts, **2) Important baseline differences:** nsaid users: more female, sl older, higher bmi, more depressive symptoms. More antidepressants, more benzos. Less likely to smoke. **3) Outcome of interest #1** They say there is a slight protective effect until age 74, but I am having trouble understanding their data.	**Comments:** reanalysis of a htn treatment trial: beta blocker, thiazide or placebo. All hypertensive and untreated at entry. Trial participants but no baseline cog testing. Mean age 70. It doesn't seem that PALT over time is sufficient to determine cog decline. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? No 2) Selection minimizes baseline

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	2651 **Duration of follow up:** 8 years for trial, **Cognitive substudy:** baseline 1983-4, nart at bl, palt and trails A **Time from risk factor assessment to final cognitive assessment:** baseline, months 1, 9, 21, 54	consent. No baseline cognitive requirements. Mean age 70. **Inclusion criteria:** Participation in the MRC treatment trial of hypertension in older adults **Exclusion criteria:** Serious cardiovascular, cerebrovascular, or other intercurrent illnesses	**Method(s) of assessing cognitive status:** change in PALT scores. **Informant interview?:** No		differences in prognostic factors? No 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? No 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Not Applicable 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Prince, Bird, Blizard, et al., 1996 MRC Trial	**Geographical location:** 226 UK locations **Setting:** Clinical – drawn from GP registries **Study design:** RCT **Test intervention:** Atenolol 50mg daily (n=640) or hctz 25mg + amiloride 2.5mg daily (n=633) adjusted to BP target range **Comparator**	**Age:** Range: 65 – 74 years **Sex:** Female: 58% Male: 42% **Race/ethnicity:** NR **Baseline cognitive status:** Normal Non-demented MCI CIND AAMI AACD	**Covariates/potential confounders adjusted for in analyses:** Age Sex Baseline cognitive status **Method(s) of assessing cognitive status:** Other – Paired associate learning test, Trails A,– administered at baseline, 1, 9, 21, and 54 months **Informant interview?:**	**1) Follow-up rate:** 88% completed at least 3 of the 5 f/u assessments **2) Important baseline differences:** No **3) Outcome of interest #1** No signficiant difference in PALT or Trails A between groups Secondary “per-protocol” analysis did not show any significant difference on the PALT or Trails A between groups	**Comments:** Mean fall in BP was 39.3 for diuretic, 31.5 for b-blocker and 14.7 for placebo. **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Partial (subjects blind/providers not blind) 4) Outcome assessors blind? Can’t Tell 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	intervention: Placebo (n=1311) **Number of participants enrolled:** 4396 overall 2584 in cognitive substudy **Duration of follow up:** Mean = 5.8 years **Time from risk factor assessment to final cognitive assessment:** 5.8 years	**Inclusion criteria:** SBP 160-209 and mean DBP < 115 mmg Hg Age 65-74 **Exclusion criteria:** Taking anti-HTN med CHF, angina, DM, asthma or other serious disease MI or CVA w/in 3 months	No		7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Can't Tell
Qiu, Winblad, Fastbom, et al., 2003 **AND** **Guo, Fratiglioni, Viitanen, et al., 2001** Kungsholmen Project	**Geographical location:** Stockholm, Sweden **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1473 in overall cohort; 966 in this analysis **Duration of follow up:** Median 5.7 years **Time from risk factor assessment to final cognitive assessment:**	**Age:** Range: ≥ 75 years **Sex:** [n (%)] Female: 727 (75%) Male: 239 (25%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age >=75 y.o Resident of Kungsholmen district APOE and baseline BP data available **Exclusion criteria:**	**Risk factor/exposure 1:** Anti-hypertensive at baseline **Method of assessing risk factor/exposure 1:** Self-report Direct measurement-bottles or prescriptions when available **Risk factor/exposure 2:** Apo# E4; HTN at baseline **Method of assessing risk factor/exposure 2:** Direct measurement	**1) Follow-up rate:** Drop-out was related to increasing age and decreased baseline MMSE **2) Important baseline differences:** Yes by APOE status **3) Outcome of interest #1** Incident AD = 204 subjects Relative risk for AD by exposure: Any E4, RR=1.6 (95% CI, 1.2-2.1) SBP <140 (reference) 140-159, RR 1.3 (0.8-2.0) >=160, RR 1.4 (0.9-2.2) DBP <70, RR 1.9 (1.2-3.0) 70-89, Reference >=90, RR 1.0 (0.7-1.4)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partially 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Median 5.7 years (range 0.1 to 8.2)	Dementia	**Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status Vascular disease SBP, DBP and antihtn drug use **Method(s) of assessing cognitive status:** 2 physicians independently made a preliminary diagnosis and 3rd opinion used for disagreements; for deceased subjects, 2 MDs made diagnosis after reviewing medical records and death certificates NINCDS-ADRDA like criteria DSM-IIIR **Informant interview?** No	Anti-HTN medication, RR 0.6 (0.5-0.9); risk reduction only noted in those with elevated SBP (>=140; RR 0.6, 95% Ci 0.4 to 0.8) or with elevated DBP (>=70, RR = 0.6, 95% CI 0.5-0.9) **4) Outcome of interest #2** Interaction terms: APOE-e4 allele combined with low DBP increased the risk of AD (RR 4.5, 95% CI 2.6-8.0), independent of anti-HTN drug use. Anti-HTN treatment reduced the risk of AD, regardless of APOE-e4 status	9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Ravaglia, Forti, Lucicesare, et al., 2008a Conselice Study of Brain Aging (CSBA)	**Geographical location:** Conselice municipality, Italy **Setting:** Community Other – also included institutionalized individuals **Study design:** Prospective cohort **Number of participants enrolled:** 749 **Duration of follow up:** Mean 3.9 (sd = 0.7) years **Time from risk factor assessment to final cognitive assessment:** Mean 3.9 (sd = 0.7) years	**Age:** Mean (SD): 73.2 (6.0) **Sex:** [n (%)] Female: 401 (53.5) Male: 348 (46.5) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Normal **Inclusion criteria:** ≥65 yrs old participant in the CSBA study **Exclusion criteria:** Individuals with baseline diagnosis of MCI, dementia, or unclassified cognitive status. Individuals with sensory/motor deficits precluding outdoor activity, missing APOE genotype or lacked follow-up info to determine cognitive status	**Risk factor/exposure 1:** physical activity a) no. of city blocks walked daily, b) no. flights of stairs climbed daily, c) frequency and duration of weekly participation during past year in occupational, recreational and sport activity **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level APOE Cardiovascular disease Hypertension Hyperhomocysteinema Cerebrovascular disease Diabetes COPD Cancer ADL motor impairment **Method(s) of assessing cognitive status:**	**1) Follow-up rate:** 749/865 **2) Important baseline differences:** NR **3) Outcome of interest #1** 54 incident AD cases 86 incident dementia total **4) Outcome of interest #2** None of the categorizations of physical activity was significantly associated with incident AD. Some HRs were above 1.0 and some were less than 1.0	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			NINCDS-ADRDA DSM Other – MCI defined as MMSE <24, not demented, ≤ 1.5 sd below age/education adjusted norms on any test, independently perform ADL/IADL **Informant interview?:** Yes		
Ravaglia, Forti, Lucicesare, et al. 2008b Conselice Study of Brain Aging	**Geographical location:** Conselice, Italy **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 864 **Duration of follow up:** years 3.9 (0.5) **Time from risk factor assessment to final cognitive assessment:** 3.9 (0.5)	**Age:** Median: NCI-72.3 (5.6) MCI- 78.1 (8.3) **Sex:** [n (%)] Female: NCI-306 (48.6) MCI- 36 (50) Male: NCI-323 (51.4) MCI- 36 (50) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age >=65 years old **Exclusion criteria:** Dementia at baseline or during f/u Major sensory – motor deficits or any psychiatric condition	**Risk factor/exposure 1:** Depression by GDS-30 >=10 at baseline **2:** Antidepressant use at baseline **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 1:** APOE genotyping **Method of assessing risk factor/exposure 1:** Direct: PCR **Covariates/potential confounders adjusted for in analyses:**	**1) Follow-up rate:** 675/864=78% After excluding incident dementia (n=78)or unclassifiable status (n=3), 595 analyzed **2) Important baseline differences:** **3) Outcome of interest #1** Incident MCI (155 subjects) GDS >=10: 1.1 (0.7 to 1.9) Antidepressant use at baseline: OR 2.9 (1.3 to 6.6) **4) Outcome of interest #2** Subgroup analyses for MCI with memory impairment (79 subjects) GDS >=10: 1.1 (0.5 to 2.0) Antidepressant use at baseline: OR 2.8 (1.0 to 7.7) **Subgroup analyses for MCI without memory impairment** (76 subjects) GDS >=10: 1.2 (0.6 to 2.3) Antidepressant use at baseline: OR	**Comments:** Very low educational status – 85% < 5 years Logistic regression analyses **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Yes 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the cohort: Yes 5) Validated method for ascertaining exposure: Yes 6) Validated method for ascertaining clinical outcomes: Yes 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Yes 9) Completeness of follow-up: Yes 10) Analysis controls for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		(other than depression) hampering a reliable cognitive assessment.	Age Sex Educational level APOE genotype Framingham stroke risk score HTN Hyperhomocysteinemia **Method(s) of assessing cognitive status:** 2-stage evaluation with neuropsychological testing Other – MCI: a) age and education adjusted score >= 1.5 SD below reference threshold on any neuropsycholgical testing; b) no need for supervision or external help in ADLs or IADLS; c) absence of DSM-IV criteria for dementia …Subclassified into MCI with objective memory impairment and MCI w/o memory impairment **Informant interview?:** No	3.1 (1.2 to 8.2) A test for interaction between baseline elevated GDS and antidepressant use was significant. Risk of MCI for both compared to no antidepressant/low GDS: OR 12.0 (95% CI 2.8 to 52.1)	confounding: Yes 11) Analytic methods appropriate: Yes
Ravaglia, Forti, Maioli, et al., 2005	**Geographical location:** Conselice, Italy **Setting:**	**Age:** Mean (SD): 74.6 (7.1) Range: ≥ 65 years **Sex:** [n (%)]	**Risk factor/exposure 1:** hcy **Method of assessing**	**1) Follow-up rate**: 816/937 87%. **2) Important baseline differences:** high hcy: older, more women, less	**Comments:** 15.3 % of subjects not actually reassessed but information from "subjects themselves, relatives, general practitioners, and death

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
AND **Ravaglia, Forti, Maioli, et al., 2007** Conselice Study of Brain Aging	Community **Study design:** Prospective cohort **Number of participants enrolled:** 937 dementia free at baseline **Duration of follow up:** 3.8 yrs (0.8) **Time from risk factor assessment to final cognitive assessment:** 3.8 yrs	Female: 563 (55%) Male: 453 (45%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Resident of Conselice Age ≥ 65 years as of 01 JAN 1999 **Exclusion criteria:** NR	**risk factor/exposure 1:** Direct measurement Fasting plasma, frozen, doesn't say how long **Covariates/potential confounders adjusted for in analyses:** age, sex, education, apoE, stroke, creatinine, folate, vit b12, smoking status, dm, htn, cardiovasc dz, bmi **Method(s) of assessing cognitive status:** DSM NINCDS-ADRDA **Informant interview?:** Yes, for those who screened positive for dementia	APOE e4, less dm, lower vit B, more smokers, more strokes, more cardiovasc dz, **3) Outcome of interest #1** HR for AD 2.08 (1.15 – 3.79)	certificates". No other details were given. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Rea, Breitner, Psaty, et al., 2005 The Cardiovascular Health Study (CHS)	**Geographical location:** 4 US communities in NC, SA, MD, & PA **Setting:** Community **Study design:** Prospective cohort **Number of**	**Age:** NR Mean 71-72 for 5888 participants in the parent study **Sex:** Female: NR Male: NR (Reported in person years)	**Risk factor/exposure 1:** Statin **Method of assessing risk factor/exposure 1:** Direct measurement – baseline use from Rx bottles; reassessed annually	**1) Follow-up rate:** > 95% HR for AD (95% CI) Adjusted for age, sex, educational level, baseline alcohol consumptin, baseline MMSE, coronary heart disease status, stroke status. Never use (216 events/1,000 person years), HR 1 (ref) Stain ever use (21 events/1,000	**Comments:** Overlapping sample with Bernick, et al., 2005, but with different outcomes reported **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	participants enrolled: 2798 **Duration of follow up:** Mean = 6 yrs **Time from risk factor assessment to final cognitive assessment:** Median 5 yrs?	**Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Living in study community; ≥ 65 yo; able to respond to questions **Exclusion criteria:** Dementia; institutionalized; CA Tx; wheelchair-bound	**Risk factor/exposure 2:** Age, sex, education level, baseline alcohol consumption, coronary heart disease, stroke status **Method of assessing risk factor/exposure 2:** Self-report **Covariates/potential confounders adjusted for in analyses:** age, sex, educational level, baseline alcohol consumptin, baseline MMSE, coronary heart disease status, stroke status. **Method(s) of assessing cognitive status:** NINCDS-ADRDA OR DSM-IV Other – Included CESD for depression **Informant interview?:** Yes	person years) HR 1.21 (0.76 to 1.91) HR for mixed AD/Vascular Dementia (95% CI) Adjusted for age, sex, educational level, baseline alcohol consumptin, baseline MMSE, coronary heart disease status, stroke status. Never use (137 events/1,000 person years), HR 1 (ref) Stain ever use (9 events/1,000 person years) HR 0.87 (0.44 to 1.72) No dose-response for duration of statin use. HR (95% CI) for AD < 1 year statin: 1.52 (0.78 to 2.98) 1 to 3 years statin: 1.05 (0.49 to 2.24) > 3 years statin: 1.04 (0.42 to 2.56) No relationship with statin lipophilia Lipophilic HR 1.03 (0.57 to 1.86) Less lipophiilic: HR 1.58 (0.80 to 3.11) Sensitivity analysis show no difference when restricted to subjects with clinical CAD or Total cholesterol >/200 mg/dl; No interactin effects between statins and - age >75 vs. younger; sex; race; smoling status, HTN, DM, clinical cerebrovascular disease, APOEe4 genotype, CRP.	3) Sample size calculated/5% difference? Yes 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Reitz, den Heijer, van Duijn, et al., 2007	**Geographical location:** Ommoord District of Rotterdam, The Netherlands	**Age:** Mean (SD): 69.5 (9.1) **Sex:** [n (%)] Female: 4221 (59.9%)	**Risk factor/exposure 1:** smoking **Method of assessing**	**1) Follow-up rate:** reports follow-up rate of 99.9% with respect to dementia **2) Important baseline differences:**	**Comments:** None **Quality assessment:** *For observational studies:*

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Rotterdam Study	**Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 6868 **Duration of follow up:** Mean follow-up 7.3 ± 4.3 yrs **Time from risk factor assessment to final cognitive assessment:** mean follow-up 7.1 yrs	Male: 2647 (40.1%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participation in the Rotterdam Study **Exclusion criteria:** Prevalent dementia; missing information on smoking history	**risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level ETOH use apoE **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes (at least for those who refused cognitive eval) or who had CAMDEX as second stage of case identification.	NR **3) Outcome of interest #1** Current smokers had greater risk of incident AD **4) Outcome of interest #2** Current smokers without an APOE e4 allele had greater risk of incident AD **5) Outcome of interest #3** Current smokers with an APOE e4 allele were not at greater risk of incident AD	1) Unbiased selection of the cohort?: yes 2) Selection minimizes baseline differences in prognostic factors?: yes 3) Sample size calculated/5% difference?: Can't tell 4) Adequate description of the cohort?: yes 5) Validated method for ascertaining exposure?: yes 6) Validated method for ascertaining clinical outcomes?: yes 7) Outcome assessment blind to exposure?: no 8) Adequate follow-up period?: yes 9) Completeness of follow-up?: yes 10) Analysis controls for confounding?: yes 11) Analytic methods appropriate?: yes
Reitz, Luchsinger, Tang, et al., 2005 WHICAP	**Geographical location:** Washington Heights, Hamilton Heights, and Inwood, in northern Manhattan, NY **Setting:** Community **Study design:** Prospective cohort	**Age:** Mean (SD): 75.6 (5.4) **Sex:** [n (%)] Female: 558 (70.5%0 Male: 233 (29.5%) **Race/ethnicity:** [n (%)] Hispanic 384 (48.6%) White 152 (19.2%) Black 250 (31.6%) DK 5 (0.6%)	**Risk factor/exposure 1:** smoking **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in**	**1) Follow-up rate:** only included subjects who have 3 waves of follow-up 791/1613 (not demented at baseline and had smoking data available) **2) Important baseline differences:** Current smokers more likely to be male and more likely to be African American **3) Outcome of interest #1**	**Comments:** Question 2 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: can't tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Number of participants enrolled: 791 **Duration of follow up:** About 5 years **Time from risk factor assessment to final cognitive assessment:** about 5 years	**Baseline cognitive status:** Normal **Inclusion criteria:** Medicare recipients ≥ 65 yo; without dementia or cognitive impairment; provided complete smoking information; had at least 3 f/u visits **Exclusion criteria:** Dementia or CIND @ baseline; smoking information unavailable; < 3 f/u visits	**analyses:** Age Race Sex Educational level HTN, Heart disease DM APOE **Method(s) of assessing cognitive status:** Other – decline on cognitive tests **Informant interview?:** No	Current or past smoking was not associated with more rapid cognitive decline in the whole sample (p = 0.2) **4) Outcome of interest #2** Current smokers > 75 years showed greater decline on memory tasks (p=0.02). There was no significant difference by smoking status for those ≤ 75 years or on any subgroup on the abstract/visuospatial tasks. **5) Outcome of interest #3** In those without an APOE e4 allele, the current smoking was associated with increased risk of decline on memory among those > 75 yrs. There was no significant difference for those ≤ 75 years, the abstract/visuospatial tasks or individuals with at least one APOE e4 allele.	4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Partially 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Reitz, Tang, Manly, et al., 2007 Washington Heights – Inwood Columbia Aging Project (WHICAP)	**Geographical location:** Northern Manhattan, NY, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1772 **Duration of follow up:** baseline (1992-94)	**Age:** Mean (SD): 76.3 (6.1) **Sex:** Female: 69.4% Male: 30.6% **Race/ethnicity:** White 22.6% Black 33.6% Hispanic 43.9% "(percentages do not total 100 because of rounding)" **Baseline cognitive**	**Risk factor/exposure 1:** HTN at baseline **Method of assessing risk factor/exposure 1:** Self-report Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age, Race, Sex Educational level, apoE4, stroke, dm,	**1) Follow-up rate:** "about half" were evaluated at the third follow up for one section (change over time) it says 79% had at least 3 intervals, 59% had 4 or more intervals, but it doesn't say if this is really the whole sample **2) Important baseline differences:** NR **3) Outcome of interest #1** risk of all cause mci with htn 1.2 (0.81 – 1.69)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Yes 6) Validated method for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	then every 18 mos. for three additional waves; mean of 4.7 years **Time from risk factor assessment to final cognitive assessment:** Mean of 4.7 years	**status:** Non-demented Not mci **Inclusion criteria:** No MCI or dementia at baseline Had at least one follow-up interval Had complete information to ascertain MCI **Exclusion criteria:** Prevalent dementia Prevalent MCI Unavailable for follow-up	heart disease, LDL level **Method(s) of assessing cognitive status:** Petersen's criteria referenced but not really **Informant interview?:** Petersen's criteria referenced but informant missing	amnestic mci 0.90 (0.54 – 1.47) nonamnestic mci 1.60 (0.93 – 2.85)	ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Reitz, Tang, Luchsinger, et al., 2004 Washington Heights – Inwood – Columbia Aging Project (WHICAP)	**Geographical location:** Northern Manhattan, NY, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 4316 **Duration of follow up:** 4.8 +/- 2.9 years **Time from risk factor assessment to final**	**Age:** Range: ≥ 65 years **Sex:** [n (%)] NR **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Medicare recipients ≥ 65 years of age Residing in northern Manhattan, NY **Exclusion criteria:** Prevalent dementia	**Risk factor/exposure 1:** Plasma lipids **Method of assessing risk factor/exposure 1:direct measurement** cholesterol and lipid profile measured by fasting blood sample obtained at initial assessment **Risk factor/exposure 2:** Diabetes mellitus **Method of assessing risk factor/exposure 2:** self-report	**1) Follow-up rate:** 1168/2126 = 54.9% **2) Important baseline differences:** NR **3) Outcome of interest #1** Total cholesterol: lower cholesterol is associated with lower risk of AD in a model adjusted for BMI, APOE, diabetes, heart disease and hypertension (trend test P=.04), but does not reach significance in a model adjusted for sex, age, education and race (trend test P=.07). No other factors reached significance in either model (Non-HDL-C, HDL-C, triglycerides or LDL-C) **4) Outcome of interest #2**	**Comments:** Analysis for diabetes and hypertension limited. Only percentage of people with DM and HTN in incident AD and control groups reported. Self report of diabetes and hypertension at baseline. Not clear if also asked at follow-up. Both hypertension and diabetes are likely to be under-identified by self-report. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5%

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	cognitive assessment: 4.8 +/- 2.9 years	Race other than those listed above No blood available	**Risk factor/exposure 3:** hypertension **Method of assessing risk factor/exposure 3:** self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Additional models adjusted for: BMI, diabetes mellitus, hypertension, heart disease and APOE4 genotype **Method(s) of assessing cognitive status:** [delete all that do not apply] NINCDS-ADRDA **Informant interview?:** NR	Diabetes- no statistics calculated. 119 cases incident AD 5 untreated diabetics (4.2%); 18 treated diabetics (15.1%) 635 control subjects. 29 untreated diabetics (3.9%) 86 treated diabetics (11.5%) **5) Outcome of interest #3** Hypertension- no statistics calculated. 119 cases incident AD 22 untreated htn (18.5%) 39 treated htn (32.8%) 635 control subjects 125 (16.8%) untreated htn 275 (36.9%) treated htn	difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Assessment of risk factor? Yes 6) Assessment cognitive outcome: Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Rondeau, Jacqmin-Gadda, Commenges, et al.,	**Geographical location:** Gironde and Dordogne, France	**Age:** At 10 yr f/u: Mean (SD): PAQUID sample: 82.5 ALMA sample: 82.3	**Risk factor/exposure 1:** exposure to aluminum in drinking water	**1) Follow-up rate:** 1925/3970 nondemented at baseline **2) Important baseline differences:** Statistical comparisons NR	**Comments:** Questions 1, 2, – no cat Dx **Quality assessment:** *For observational studies:*

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
2009 PAQUID	**Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1925 **Duration of follow up:** 11.3 yrs (mean) **Time from risk factor assessment to final cognitive assessment:** Uncertain, but estimated range from 0-8 yrs (Not entirely clear that all exposure data collected prior to time point for final cognitive outcome)	**Sex:** [n (%)] Female: 1,181 (61.4) Male: 744 (38.6) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age ≥65, living at home, in specific region of France **Exclusion criteria:** None except as covered by inclusion criteria	**Method of assessing risk factor/exposure 1:** Self-report Other – chemical analyses of drinking water in geographic area **Covariates/potential confounders adjusted for in analyses:** Age Gender Educational level Wine consumption Place of residence (urban vs rural) Cohort (ALMA or PAQUID) **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM Other – change over time on MMSE **Informant interview?:** No	**3) Outcome of interest #1** Greater decline on MMSE for every 0.1 mg/day higher aluminum intake based on daily consumption (p=0.001) or geographic exposure (<0.001). Silica intake was not associated with cognitive decline. Associations no longer significant when the demented were excluded suggesting that aluminum intake only associated with decline as part of the dementing process. **4) Outcome of interest #2** RR = 1.34 (95% CI: 1.09-1.65) – increased risk of AD for ≥0.1mg/day consumption of aluminum. No dose-response relationship **5) Outcome of interest #3** R=0.88 (95% CI: 0.79-0.99) lower risk of AD for each 10 mg/day higher intake of silica Exposure to aluminum or silica based on geographic exposure not associated with AD	1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Partial 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Rovio, Kareholt, Helkala, et al., 2005 Cardiovascular risk	**Geographical location:** Kuopio & Joensuu, Finland **Setting:** Community	**Age:** At midlife exam: Mean (SD): 50.6 (6.0) Range: 39-64 At re-examination: Mean (SD): 71.6 (4.1)	**Risk factor/exposure 1:** Leisure-time physical activity at midlife **Method of assessing risk factor/exposure**	**1) Follow-up rate:** 1449 of 2000 randomly selected (72.5%) participated. 434 refused f/u, and 107 refused due to poor health (total refusals = 551). F/U rate not calculable	**Comments:** Rovio 2007 updates this analysis **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
factors, Aging and Incidence of Dementia (CAIDE) study North Karelia Project FINMONICA study	**Study design:** Prospective cohort Sampled once at midlife (1972, 1977, 1982 or 1987) and again in 1998 **Number of participants enrolled:** 1449 of 2000 randomly selected (72.5%) **Duration of follow up:** 21 yrs (SD 4.9) **Time from risk factor assessment to final cognitive assessment:** 21 yrs (SD 4.9)	Range: 65-79 **Sex:** Female: 900 (62.1%) Male: 549 (37.9%) **Race/ethnicity:** NR **Baseline cognitive status:** NR but unlikely had cognitive impairment in midlife at baseline **Inclusion criteria:** Survivors of 4 separate samples of the North Karelia Project and FINMONICA study, lived in 2 geographically defined areas; complete data on outcome, physical activity, and covariates. **Exclusion criteria:** NR	**1:** Self-report: "How often do you participate in leisure-time physical activity that lasts at least 20-30 minutes and causes breathlessness and sweating?" "active" = active $\geq$ 2 times/wk "sedentary" = < 2 times/wk **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level f/u time locomotor disorders APOE Clinical variables Smoking status Alcohol use **Method(s) of assessing cognitive status:** MMSE for screening (<24 MMSE score) NINCDS-ADRDA DSM-IV **Informant interview?:** No	**2) Important baseline differences:** Those who were sedentary were slightly younger at baseline and slightly longer f/u interval. Relatively more women than men were sedentary. **3) Outcome of interest #1** 61 incident cases of dementia (48 had AD) **4) Outcome of interest #2** Dementia (n=1251) Crude OR 0.55 (95% CI, 0.30-1.01) Fully adjusted OR 0.47 (0.25-0.90) **5) Outcome of interest #3** AD (n=1239) Physical activity reduced the risk of AD in all 4 models (crude and 3 adjusted). Active individuals had approximately 60% lower odds of AD than sedentary ones. Crude OR 0.45 (95% CI, 0.22-0.93) Fully adjusted OR 0.35 (0.16-0.80) Physical activity had same effect on both sexes. APOE appears to be an effect modifier: among APOE carriers there is an association between physical activity and AD, but not among non-carriers.	2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No (exercise assessment) 6) Validated method for ascertaining clinical outcomes? Partial. Only those with MMSE<24 had full evaluation. 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Rovio, Kareholt, Viitanen, et al., 2007 Cardiovascular risk factors, Aging and Incidence of Dementia (CAIDE) study North Karelia Project FINMONICA study	**Geographical location:** Kuopio & Joensuu, Finland **Setting:** Community **Study design:** Prospective cohort Sampled once at midlife (1972, 1977, 1982 or 1987) and again in 1998 **Number of participants enrolled:** 1449 **Duration of follow up:** Mean: 20.9 years (SD 4.9) **Time from risk factor assessment to final cognitive assessment:** 21 years (mean)	**Age:** <u>At midlife exam:</u> Mean (SD): 50.4 (6.0) Median: Range: 39-64 <u>At re-examination:</u> Mean (SD): 71.3 (4.0) Median: Range: 65-79 **Sex:** Female: 900 (62.1%) Male: 549 (37.9%) **Race/ethnicity:** NR **Baseline cognitive status:** NR, but unlikely they were impaired at baseline in midlife **Inclusion criteria:** Survivors of 4 separate samples of the North Karelia Project and FINMONICA study; lived in two geographically defined areas; complete data on outcome, physical activity, and covariates **Exclusion criteria:** NR	**Risk factor/exposure 1:** Work-related physical activity **Method of assessing risk factor/exposure 1:** Self-report <u>Occupational physical activity</u>: "How physically heavy is your work?" Dichotomized to sedentary vs. active groups. Dichotomization point NR. <u>Total daily commuting physical activity</u>: "How many minutes do you walk, bicycle, or have some other physical activity when you are going to and from work?" Categorized: 1) not at all 2) $\leq$ 59 minutes 3) $\geq$ 60 minutes **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level	**1) Follow-up rate:** 1449 of 2000 randomly selected (72.5%). Remaining 27.5% "non-participants." Missing data on independent variables in 291 persons. Analytical sample = 1158 (57.9%) **2) Important baseline differences:** NA **3) Outcome of interest #1** 44 incident cases of dementia (33 AD). **4) Outcome of interest #2** Neither occupational (OR, 1.90; 95% CI, 0.73-4.95) nor commuting physical activity (OR, 0.48; 95% CI 0.09-2.58) were associated with the risk of AD.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? No 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			F/u time Locomotor symptoms Occupation Income at midlife Leisure physical activity APOE Vascular disorder Smoking status **Method(s) of assessing cognitive status:** MMSE for screening (screen + if score ≤24) NINCDS-ADRDA DSM-IV **Informant interview?:** No		
Ryan, Carriere, Scali, et al., 2009 ESPRIT substudy	**Geographical location:** Montpelier, France **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 996 **Duration of follow up:** 4 yrs **Time from risk factor assessment to final**	**Age:** Mean (SD): 72.8 (5.5) **Sex:** [n (%)] Female: 996 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥65 yrs, non-institutionalized and resided in Montpelier, France	**Risk factor/exposure 1:** lifetime estrogen exposure **Method of assessing risk factor/exposure 1:** Self-report of reproductive factors associated with estrogen exposure and use of exogenous hormone treatment **Covariates/potential confounders adjusted for in analyses:**	**1) Follow-up rate:** 996/1277 of non-demented at baseline **2) Important baseline differences:** NR **3) Outcome of interest #1** In fully adjusted model, no association between lifetime estrogen exposure and risk of substantial decline on any cognitive measures	**Comments:** Question 2 – cat Dx **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	cognitive assessment: Lifetime	**Exclusion criteria:** None except as covered by exclusion criteria	Age Educational level Marital status Depressive symptoms Caffeine intake Physical impairment Medical conditions Baseline cognitive status **Method(s) of assessing cognitive status:** DSM Other – substantial decline on cognitive tests defined as lowest quintile of the difference between baseline score and score at either of the follow-up visits **Informant interview?:** No		7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Saczynski, Pfeifer, Masaki, et al., 2006 HAAS Honolulu Asia Aging Study	**Geographical location:** Honolulu, Hawaii **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3,508 **Duration of follow up:** 27.5 (mean) yrs for midlife social measures and 4.6 (mean) yrs for late life **Time from risk factor assessment to final cognitive assessment:** 27.5(mean) yrs for midlife social measures and 4.6 (mean) yrs for late life	**Age:** Mean (SD): 76.8 years **Sex:** [n (%)] Female: 0 (0%) Male: 2513 (100%) **Race/ethnicity:** [n (%)] All of Japanese origin. **Baseline cognitive status:** Non-demented **Inclusion criteria:** Japanese-American men born between 1900 and 1919 who were living on the island of Oahu, Hawaii, at the time of enrollment in 1965 **Exclusion criteria:** Those who had dementia at the 1991 exam were excluded from the incident cohort.	**Risk factor/exposure 1:** Social engagement **Method of assessing risk factor/exposure 1:** Self-report marital status; living arrangement; participation in social, political, or community groups; participation in social events with coworkers; and the existence of a confidant relationship (composite score of the above) **Covariates/potential confounders adjusted for in analyses:** Age Education Cognitive Abilities Screening Instrument score, apolipoprotein E e4 allele status, History of stroke, coronary heart disease, depression, and disability **Method(s) of assessing cognitive status:** NINCDS-ADRDA	**1) Follow-up rate:** Of 3,508, 521died before examination 5, 359 did not participate in examination 5, and 115 had missing data Final sample: 2,513 men Excluding those who died, rate of follow up was 84.13% **2) Important baseline differences:** Compared with men who died or dropped out of the sample, those who survived were younger and had higher CASI scores, more education, less cerebrovascular disease , less coronary heart disease, and less impairment in activities of daily living. Those with low mid-life or late-life social engagement scores were older at baseline. **3) Outcome of interest #1** 222 men diagnosed with incident dementia, 134 (60%) had Alzheimer's disease, 47 had vascular dementia, and 41 had other types of dementia **4) Outcome of interest #2** Midlife social engagement not associated with incident dementia. Compared to those who had highest social engagement in late life, those who had the lowest social engagement had a higher risk of developing dementia. HR= 2.34 (1.18, 4.65)	**Comments:** Question 1 Results presented for all cause dementia. No individual results for AD though the text mentions that they analyzed AD separately and found similar results. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			DSM **Informant interview?:** Yes	**5) Outcome of interest #3** Compared to those who had consistently high social engagement in mid and late life, those whose social engagement decreased from mid to late life had a higher risk of incident dementia. HR= 1.87 (1.12, 3.13)	
Saxby, Harrington, Wesnes, et al., 2008 Study on Cognition and Prognosis in the Elderly (SCOPE)	**Geographical location:** Tyneside, UK (one site from a multi-center trial) **Setting:** Clinical **Study design:** RCT **Test intervention:** Candesartan 8-16mg; mean dose = 12 mg Other antihypertensives allowed **Comparator intervention(s):** Placebo, other antihypertensives allowed **Number of participants enrolled:** 257; 228 available for analysis **Duration of follow up:**	**Age:** Mean: 76 years Range: 70 – 89 years **Sex:** [n (%)] (of those available for analysis) Female: 107 (47%) Male: 121 (53%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** eliminated theoretically those who had mmse < 24 or who had sig decline in cdr and iqcode but no one was actually eliminated using these criteria **Inclusion criteria:** Hypertensive 70 – 89 years **Exclusion criteria:** MMSE score < 24 Reported significant decline in cognitive	**Covariates/potential confounders adjusted for in analyses:** age, number of errors on the New Adult Reading Test, baseline cognitive performance **Method(s) of assessing cognitive status:** change in test score measured every 12 months in 5 domains: Episdoic memory (5 tests); Attention (3 tests); Working memory (2 tests); Speed of cognition (# tests not given); Executive function (4 tests) **Informant interview?** no	**1) Follow-up rate:** 159/228 completed maximum number of assessments – 70%; 228/257 analyzed = 88.7%, average proportion of the follow up period spent on active tx was 88% **2) Important baseline differences:** “no baseline difference between the candesartan and placebo groups” **3) Outcome of interest #1** change in cognition between the candesartan and placebo groups as measured by coef of decline on five composite factor factor scores significant for attn (candesartan = 0.004 vs. placebo -0.036, effect size = 0.28, p= 0.04) and episodic memory (0.14 vs. -0.22, effect size = 0.28, p=0.04) but not for speed of cognition, working memory or executive functioning.	**Comments:** subj 70-89 yrs old, sbp 160 – 179 mmHg, dbp 90-99 mmHg or both For scope overall, hctz was added to 49% of candesartan group and 66% of the control group. One site from a multi-center trial (see Skoog, Lithell, Hansson, et al., 2005); only 257 out of 4937 participants included in analysis. **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Can’t Tell (double-blind but specific blind not specified) 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? No. AstraZenac sponsored, but not involved in analysis.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	mean 44 mos, (12), range 12 – 60 mos **Time from risk factor assessment to final cognitive assessment:** rct administered meds	function			9) Randomization adequate? Yes 10) Allocation concealment adequate? Can't Tell
Scarmeas, Levy, Tang, et al., 2001	**Geographical location:** Manhattan, NY **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1772, from 2126 of 3452 initially eligible persons. **Duration of follow up:** Mean 2.9 yrs (range: 0-7.2) **Time from risk factor assessment to final cognitive assessment:** Mean 2.9 yrs (range: 0-7.2)	**Age:** Incident dementia: 78.2 ± 6.5 No incident dementia: 75.3 ±6.2 **Sex:** Females: Incident dementia: 69% No incident dementia: 68% Males: Incident dementia: 31% No incident dementia: 32% **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Cohort identified from a	**Risk factor/exposure 1:** Leisure activities **Method of assessing risk factor/exposure 1:** Self-report. Asked about 13 different activities. When dichotomized, "low"= ≤6 and "high" = >6 **Covariates/potential confounders adjusted for in analyses:** Ethnicity Sex Educational level Occupation Clinical variables **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM Other – Care Diagnostic Interview, clinical evaluation,	**1) Follow-up rate:** 2126 initially selected. 327 demented at 1st eval and excluded, leaving 1799. Leisure activity available for final sample of 1772. 1772/2126 = 83% **2) Important baseline differences:** NA **3) Outcome of interest #1** 207 incident cases of dementia (153 with probable or possible AD) **4) Outcome of interest #2--dementia** With activity as a continuous variable in an age-stratified Cox model, higher scores were associated with a reduced risk of dementia (RR, 0.88; 95% CI, 0.83-0.93). Associate remained after adjusting for ethnicity, education, and occupation. There appears to be a synergistic effect of leisure activities and education, and leisure activities and occupation. **5) Outcome of interest #3--AD**	**Comments:** All of the results are for dementia, but the authors make conclusions about AD. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Partial 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		probability sample of Medicare beneficiaries residing in northern Manhattan. 65 years or older, non-demented, seen for at least one follow-up evaluation. **Exclusion criteria:** Recent h/o stroke or Parkinson's Disease	neuropsych eval. **Informant interview?:** No	No results about AD other than reporting that 153 participants had probable or possible AD at f/u, and that 27 had possible AD with concomitant stroke.	
Scarmeas, Luchsinger, Schupf, et al., 2009 WHICAP	**Geographical location:** New York, New York **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1880 **Duration of follow up:** Mean (sd): 5.4 (3.3) yrs **Time from risk factor assessment to final cognitive assessment:** NR	**Age:** Mean (SD): 77.2(6.6) **Sex:** [n (%)] Female: 1293 (69) Male: 587 (31) **Race/ethnicity:** [n (%)] White 531 (28) Black 605 (32) Hispanic 715 (38) Other 29 (2) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Cohort identified from a probability sample of Medicare beneficiaries residing in northern Manhattan. 65 years or older, non-demented, seen for at least one follow-up evaluation.	**Risk factor/exposure 1:** Physical activity and nutrition **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level BMI Smoking Depression Leisure activities Comorbid medical conditions Baseline CDR score APOE Interval between 1st	**1) Follow-up rate:** 1880/2247 with dietary and physical activity data **2) Important baseline differences:** Less physically active individuals were more likely to be female, older, Hispanic, smokers, depressed, less educated, had a lower total caloric intake, higher BMI, more comorbid illnesses, and adhered less to the diet. **3) Outcome of interest #1** Considered simultaneously, both adherence to a Mediterranean-type diet (compared with low diet score) HR for middle diet score was 0.98 [95% CI, 0.72-1.33]; the HR for high diet score was 0.60 [95% CI, 0.42-0.87]; *P*=.008 for trend) and physical activity compared with no physical activity, the HR for some physical activity was 0.75 [95% CI, 0.54-1.04]; the HR for much physical activity was 0.67 [95% CI, 0.47-0.95]; *P*=.03 for trend) were associated with lower AD	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Yes 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		Exclusion criteria: NR	dietary and 1st physical activity measure Caloric intake **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** No	risk. **4) Outcome of interest #2** Compared with individuals neither adhering to the diet nor participating in physical activity (low diet score and no physical activity; absolute AD risk of 19%), those both adhering to the diet and participating in physical activity (high diet score and high physical activity) had a lower risk of AD (absolute risk, 12%; HR, 0.65 [95% CI, 0.44-0.96]; *P*=.03 for trend).	
Scarmeas, Stern, Mayeux, et al., 2009 WHICAP subsets	**Geographical location:** Northern Manhattan, NY **Setting:** Community **Study design** Prospective cohort **Number of participants enrolled:** 1875 1393 cog normal 482 MCI **Duration of follow up:** 4.5 (2.7) years range 0.9-16.4 yrs **Time from risk factor assessment to final cognitive assessment:** evaluated every 1.5 yrs	**Age:** Mean (SD): 76.9 (6.5) Cog norm 76.7 (6.5) MCI 77.5 (6.6) **Sex:** [n (%)] Female: 1272 (68%) Cog norm 946 (68%) MCI 326 (68%) Male: 603 (32%) Cog norm 447 (32%) MCI 156 (32%) **Race/ethnicity:** [n (%)] White 558 (30%) Cog norm 434 (31%) MCI 124 (26%) Black 623 (33%) Cog norm 479 (34%) MCI 144 (30%) Hispanic 687 (36%) Cog norm 473 (34%) MCI 214 (44%) Other 7 (1%) Cog norm 7 (1%) MCI 0 (0%)	**Risk factor/exposure 1:** Mediterranean diet **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age, Race, Sex, education, apoE, bmi, time betw dietary assessment and cog assessment, **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM Mci dx'd retrospectively	**1) Follow-up rate:** subject pool selected from larger study cohort on basis on cognitive status and follow up. **2) Important baseline differences:** Hispanic subjects adhered more to med. Diet. Black subj adhered less, higher adherence associated with lower caloric intake. **3) Outcome of interest #1** using lowest tertile of adherence as reference, middle tertile had hr 0.83 (0.62 – 1.12), highest tertile hr 0.72 (0.52-1.00) for development of mci **4) Outcome of interest #2** for progression from mci to ad, middle tertile hr 0.55 (0.34 – 0.90), highest tertile hr 0.52 (0.30 – 0.91)	**Comments:** Questions 1 & 2 – yes cat Dx Diagnosis of mci applied retrospectively. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? No 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	time between cog assessment and dietary assessment	**Baseline cognitive status:** Non-demented **Inclusion criteria:** Participated in either 1992 or 1999 WHICAP study, Medicare beneficiary, residing in a designated geographic area of northern Manhattan, NY **Exclusion criteria:** NR	**Informant interview?:** No		10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Scarmeas, Stern, Tang, et al., 2006 WHICAP	**Geographical location:** Northern Manhattan, NY, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2,258 **Duration of follow up:** Mean= 4.0 (3.0) yrs Range = 0.2-13.9 yrs **Time from risk factor assessment to final cognitive**	**Age:** Mean (SD): 77.2 (6.6) **Sex:** [n (%)] Female: 1514 (68) Male: 720 (32) *N slightly different than total N due to non-AD dementia* **Race/ethnicity:** [n (%)] AA 722 (32) White 620 (28) Hispanic 848 (38) Other 36 (2) *N slightly different than total N due to non-AD dementia* **Baseline cognitive status:** Non-demented	**Risk factor/exposure 1:** Mediterranean diet **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Sample cohort APOE Caloric intake Smoking Medical comorbidity	**1) Follow-up rate:** 2258/2784 (denominator excludes those who did not participate in fup due to death) **2) Important baseline differences:** Ind who developed dementia were older, less educated, and had higher BMI. Among those who developed dementia, there was a higher proportion of Hispanics and a lower proportion of whites. **3) Outcome of interest #1** Higher adherence to a Mediterranean diet was associated with decrease in risk of AD: Continuous measure of Mediteranean diet (HR=0.91; 0.83-0.98) Categorical measure: High tertile (HR=0.60; 0.42-0.87)	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment: Estimated – 2.5 yrs – risk factor data collected at 1st follow-up and follow-ups were every 1.5 yrs	**Inclusion criteria:** Medicare recipients age ≥65 residing in Northern Manhattan. Two separate cohorts were used WHICAP 1992 and WHICAP 1999. **Exclusion criteria:** None	index BMI **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** No		9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Schaefer, Bongard, Beiser, et al., 2006 Framingham	**Geographical location:** Framingham, MA, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 899 **Duration of follow up:** 9.1 yrs **Time from risk factor assessment to final cognitive assessment:** 9.1 yrs	**Age:** Mean (SD): 76 (5.0) yrs **Sex:** [n (%)] Female: 571 (63.5) Male: 328 (36.5) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** In 1948, men and women between the ages of 30 and 62 from the town of Framingham, MA followed with biennial exams since **Exclusion criteria:** none	**Risk factor/exposure 1:** DHA **Method of assessing risk factor/exposure 1:** Direct measurement Self-report **Method of assessing risk factor/exposure 2:** Self-report Proxy report Direct measurement Medical record Other **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level APOE	**1) Follow-up rate:** difficult to get meaningful numbers. 899 had plasma measures out of the 1208 that completed the wave of data collection used as the baseline for these analyses. Then subjects followed until point of censoring. **2) Important baseline differences:** NR **3) Outcome of interest #1** Ind in upper quartile of baseline plasma PC DHA levels, compared to lower 3 quartiles, did not have sig lower risk of AD (RR=0.61; 0.31–1.18). Results for all dementia were significant (RR=0.53; 0.29-0.97) **4) Outcome of interest #2** Ind in upper quartile of dietary intake of DHA, compared to lower 3 quartiles, did not have sig lower risk of AD (RR=0.63; 0.23-1.72) **5) Outcome of interest #3** Ind who consumed fish > twice a	**Comments:** Question 1 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Homocysteine **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes	week compared to those who consumed fish ≤ twice a week did not have sig lower risk of AD (RR=0.61; 0.28-1.33)	
Schuit, Feskens, Launer, et al., 2001 Zutphen Elderly Study Seven Countries Study	**Geographical location:** Zutphen, Netherlands **Setting:** NR. 88% lived independently at home. **Study design:** Prospective cohort **Number of participants enrolled:** 560 – 347 analyzed **Duration of follow up:** 3 years **Time from risk factor assessment to final cognitive assessment:** 3 years	**Age:** Mean (SD): 74.6 ±4.3 **Sex:** Female: 0 Male: 347 (100%) **Race/ethnicity:** NR **Baseline cognitive status:** Did not appear to exclude those with cognitive impairment **Inclusion criteria:** Participants in the Seven Countries Study aged 65-84 at baseline living in Zutphen. **Exclusion criteria:** NR	**Risk factor/exposure 1:** Physical activity **Method of assessing risk factor/exposure 1:** Self-report. Validated questionnaire for measuring physical activity in elderly men. Summed score for total weekly activity. Categorized: 1) ≤30 min/day 2) 31-60 min/day 3) > 60 min/day **Risk factor/exposure 2:** APOE phenotype. **Method of assessing risk factor/exposure 2:** Direct measurement; Isoelectric focusing followed by immunoblotting.	**1) Follow-up rate:** 347 of 560 (62%). No information provided on non-responders. Non-response associated with: lower SES, and health status **2) Important baseline differences:** NA **3) Outcome of interest #1—Physical activity and CD** Age and education adjusted OR (95% CI) for cognitive decline, with > 60 min/day as the reference: < 30 min/day: OR 2.0 (0.7-5.6) 31- 60 min/day: OR 1.8 (0.6-5.1) **4) Outcome of interest #2—Interaction of physical activity and APOE with CD – subgroup analysis** The OR of cognitive decline among inactive (<=1 hr/day) vs active (>1 hr/day) APOE e4 non-carriers: (OR, 0.9; 95%CI, 0.2-3.2) APOE e4 carriers: (OR, 3.7; 95%CI,	**Comments:** OR for cognitive decline was 2.0 but not statistically significant in analyses that did not include APOE as an effect modifier. At baseline, 13.5% of subjects had MMSE <=25 **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Can't tell (inadequate reporting) 2) Selection minimizes baseline differences in prognostic factors?: Can't tell (inadequate reporting) 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partially (incomplete description of cohort, but some baseline measure reported in Table 1) 5) Validated method for ascertaining exposure?: Partially (authors claim that the assessment is valid)

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Covariates/potential confounders adjusted for in analyses: Age Sex Educational level Smoking Alcohol Baseline cognitive function Clinical variables Disabilities in ADL Health status **Method(s) of assessing cognitive status:** Cognitive decline defined as a decrease of >3 points on the MMSE. **Informant interview?:** No	1.1-12.6)	6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't tell 8) Adequate follow-up period?: can't tell 9) Completeness of follow-up?: No (f/u rate of 62%) 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes
Seeman, Lusignolo, Albert, et al., 2001 McArthur Study of Healthy Aging	**Geographical location:** Durham NC East Boston MA New Haven CT **Setting:** Community **Study design:** Prospective cohort **Number of**	**Age:** Mean (SD): 74 **Sex:** [n (%)] Female: 632 (55.2%) Male: 513 (44.8%) **Race/ethnicity:** [n (%)] AA 206 (18%) White 940 (82%) **Baseline cognitive status:**	**Risk factor/exposure 1:** Respondents' perception of their social network using the MacArthur battery which had both qualitative and quantitative components. **Method of assessing risk factor/exposure**	**1) Follow-up rate**: Of 1189, 273 (23%) died before follow up. Of the remaining 916, 722 completed face to face interviews, 107 (11.7% had proxy partial interviews) and the rest refused or could not be contacted. 1145 had complete baseline data and were included in the analyses **2) Important baseline differences:** At baseline, among other differences noted, men had higher income and	**Comments:** This population is selective in that the participants were among the top one-third of their age group for functional and cognitive status at baseline. Applicability to general population may be limited. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	participants enrolled: 1189 participated 1145 analyzed **Duration of follow up:** 7.4 YEARS SD= 4.7 months **Time from risk factor assessment to final cognitive assessment:** Mean of 7.4 years.	Participants who scored in the top third of the cognitive and physical screening tests for their age group. **Inclusion criteria:** Age between 70-79 Physical: 1)No. reported disability on the 7-item activities of living scale. 2))No more than 1 reported mild disability on eight items tapping gross mobility and range of motion 3)Ability to maintain semi tandem balance for at least 10 s 4) Ability to stand from seated position at least 5 times in 20 s. Cognitive: 1) Scoring at least 6 or more on the SPSMQ 2) Remembering three or more of the six elements on a delayed recall of a short story. **Exclusion criteria:** NR	**1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Income Number of reported chronic illnesses Pulmonary function Amount of strenuous leisure activity. Amount of strenuous yard/house maintenance. Depressive symptoms Self efficacy beliefs. **Method(s) of assessing cognitive status:** Other – Language 18 item Boston Naming test Abstraction: 4 items from the Similarities subtest of the Wechsler's Adult intelligence scale Spatial ability: Copying image Incidental recall of confrontation naming Delayed recall of a story	reported more social ties overall but women reported greater involvement in groups. **3) Outcome of interest #1** After controlling for covariates, greater baseline social support was not associated with greater decline on a cognitive summary score at 7.5 year follow up: b= 1.26 p= .07. When the model was reduced by excluding baseline cognitive status and other sociodemographic factors, health status, behavioral and psychological variables, the relationship between baseline emotional support and cognitive decline became significant; b= 1.20, p= 0.05. **4) Outcome of interest #2** Being married (b= - 0.48, p= 0.52); Number of close ties (- 0.02, p=0.75); number of groups(- 0.13, p =0.70) were not significant predictors of cognitive decline over the same time period.	differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial (but standard for the field at the time) 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Informant interview?: Yes Proxy interviews were conducted for some who had missing data.		
Seshadri, Beiser, Selhub, et al., 2002 Framingham	**Geographical location:** Framingham, MA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1092 **Duration of follow up:** median 8 yrs (range 1 to 13) **Time from risk factor assessment to final cognitive assessment:** 8 years on average	**Age:** Mean (SD): 76 **Sex:** [n (%)] Female: 667 Male: 425 **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participation in the Framingham Study **Exclusion criteria:** Dementia	**Risk factor/exposure 1:** hcy **Method of assessing risk factor/exposure 1:** Direct measurement Plasma, frozen, fasting status not indicated so most likely not. **Covariates/potential confounders adjusted for in analyses:** age, sex, apoE, folate and vitamins b12 and b6, education, stroke, smoking, alcohol, dm, bmi sbp at baseline **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM In subjects with abnormal MMSE screen **Informant interview?:** Yes	**1) Follow-up rate:** 77% of those alive who had been free of dementia participated in this baseline visit **2) Important baseline differences:** NR **3) Outcome of interest #1** **Dementia n=111 (83 AD)** For each 1 SD increase in log-transformed homocysteine, RR of AD fully adjusted for total hcy 1.8(1.3 – 2.5) For homocysteine>14 umol/l , adjusted HR = 1.9 (95% CI 1.2-3.0) **4) Outcome of interest #2** No association between folate, B12, B6 and incident AD (data not given)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial, would like baseline comparison based on hcy 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes but in fully adjusted model, there were only 54 AD cases and a lot of covariates 11) Analytic methods appropriate? Partial, may have overfit models given number of cases

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Shadlen, Larson, Wang, et al., 2005 ACT	**Geographical location:** Seattle, WA **Setting:** Other - HMO **Study design:** Prospective cohort **Number of participants enrolled:** 2581 enrolled from ACT 2410 declared race 2168 had APOE data 2140 were analyzed @ f/u **Duration of follow up:** 3.29 years (1.36) **Time from risk factor assessment to final cognitive assessment:** 3.29 years (1.36)	**Age:** (from 2410 @ baseline) Mean (SD): 75.4 (6.2) Range: 65 - >85 **Sex:** [n (%)] (from 2410 @ baseline) Female: 1431 (59.4%) Male: 979 (40.6%) **Race/ethnicity:** [n (%)] (from 2410 @ baseline) White 2307 (95.7%) Black 103 (4.3%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Enrolled in ACT study; free of dementia; not institutionalized; age ≥65, member of Group Health Cooperative (HMO) **Exclusion criteria:** Dementia, living in nursing home	**Risk factor/exposure 1:** APOE **Method of assessing risk factor/exposure 1:** Direct measurement **Risk factor/exposure 2:** education **Method of assessing risk factor/exposure 2:** Self-report **Risk factor/exposure 3:** Depression **Method of assessing risk factor/exposure:** CES-D **Risk facot/exposure 4:** Diabetes mellitus **Method of assessing risk factor/exposure:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age	**1) Follow-up rate:** 2140 with APOE and f/u data. Difficult to extract exact f/u rate. 165 discontinued and 366 died during study = 75.2% f/u rate **2) Important baseline differences:** NR **3) Outcome of interest #1** Education as a continuous measure was not associated with cognitive decline. **4) Outcome of interest #2** Compared to individuals without an APOE4 allele, individuals with a single APOE4 allele did not have greater CASI decline. But individuals with two APOE4 alleles experienced greater decline in cognitive performance and the magnitude of that decline decreased as years of educational attainment increased. (coefficient =0.51 (95% CI 0.12, 0.91; *P* = 0.011)). Generalized estimating equation analysis (GEE) Risk factors associated with change in global cognitive performance No E4 reference One E4 allele coef=-0.23 (-2.5, 2.05) P=0.846 Two E4 alleles coef=-10.08 (-16.24, -3.92) P=0.001	**Comments:** Q2 – no cat Dx Depressive symptoms assessed at last f/u; therefore these results cross-sectional and not used. At 4-yr f/u, 138 (6%) of the original sample had declines in their CASI scores by 1.5 standard deviations (7 points) or greater. Subjects who were diagnosed with dementia during the study were not included in analysis. Author's Conclusions: Lower education was associated with steep 4-yr cognitive decline for APOE4 homozygotes but not for APOE4 heterozygotes. Potentially modifiable host factors such as education could influence the association of high-risk genotypes and cognitive decline. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Race Sex Years of followup Depression Diabetes Hypertension Cerebrovascular disease **Method(s) of assessing cognitive status:**] NINCDS-ADRDA DSM Other – longitudinal change in CASI score **Informant interview?:** No	Interaction of APOE4 and education One E4 x education coef .002 (-.15, .16) P=.976 Two E4 x education coef 0.51 (.12, .91) P=.011 **Outcome of interest #3** Generalized estimating equation Diabetes mellitus No-reference Yes- coef -.59 (-1.14, -.04) P=.001	6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Shah, Wilson, Bienias, et al., 2006 Religious orders study	**Geographical location:** 40 groups across US **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 990 in study overall; 824 in this analysis **Duration of follow up:** mean of 6.5 annual clinical evaluations **Time from risk factor**	**Age:** Mean (SD): 75 (7) **Sex:** [n (%)] Female: 569 (69%) Male: 255 (31%) **Race/ethnicity:** [n (%)] White 750 (91%) Other 74 (9%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participation in Religious Orders Study; agreement to annual clinical	**Risk factor/exposure 1:** htn **Method of assessing risk factor/exposure 1:** Direct measurement two sitting and one standing bp averaged also figured orthostatics and did self report. **Covariates/potential confounders adjusted for in analyses:** Age, Sex, education, presence of apoE4,	**1) Follow-up rate:** 98% did at least one follow up. 98% of possible clinical evaluations done also. (23 died before first f/u; 47 recent enrollees and not due for annual f/u) **2) Important baseline differences:** bp analyzed as a continuous variable so didn't really compare two groups. **3) Outcome of interest #1** 151 incident cases of AD In a fully adjusted model (presence of apoE4, use of antihypertensive meds), a "null relationship persisted" but results not shown. In age, sex and education adjusted model, the relative risk of 1 mmHg increase in	**Comments:** Questions 1 and 2 Probable selection bias: BP measured in older adults w/o dementia; If HTN a risk factor, those with longstanding HTN may have died prior to cohort assembly **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial 5) Validated method for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment to final cognitive assessment: NR, annual assessments	evaluations; no dementia @ baseline **Exclusion criteria:** No f/u evaluation	use of antihypertensive meds. **Method(s) of assessing cognitive status:** NINCDS-ADRDA Other: change in performance on cognitive tests over time **Informant interview?:** No	sbp was 0.995 (0.986-1.004) and for dbp 1.0 (0.985-1.015) Further analyses, using history of HTN, quadratic terms for SBP and DBP, JNC VII categories of HTN, and sitting BP only, there was no association with incident AD **4) Outcome of interest #2** Again when examining cognitive decline, in a fully adjusted model "the null relationship persisted" but results are not shown. In evaluation using covariates for age, sex, education, sbp x time had estimate of 0.00 with SE 0.00 and p =0.237, dbp x time had estimate 0.000 with SE 0.001 and p = 0.232. time itself had decrease of 0.036 points per year in global score.	ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Shumaker, Legault, Kuller, et al., 2004 Women's Health Initiative Memory Study (WHIMS)	**Geographical location:** North America **Setting:** Clinical **Study design:** RCT **Test intervention:** CEE (0.625mg) **OR** CEE + MPA (2mg)	**Age:** Range: 65 – 79 years **Sex:** [n (%)] Female: 7479 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] White, non-white; overall statistics not reported **Baseline cognitive status:** Non-demented	**Risk factor/exposure 1:** CEE or matching placebo Also combined data with CEE + MPA trial **Method of assessing risk factor/exposure 1:** Other – RCT **Risk factor/exposure 2:** CEE + MPA or matching placebo	**1) Follow-up rate:** At year 6 CEE alone 539 of 1464 (36.8%) Placebo 518 of 1483 (34.9%) CEE or CEE+MPA 550 of 3693 (14.9%) Or total placebo 539 of 3786 (14.2%) Adherence at year 6 was 42% for HRT and 47.8% for placebo. **2) Important baseline differences:** Higher prevalence of hypertension in CEE group (p=.01) Comparing CEE alone vs CEE + MPA: women receiving CEE alone were less educated, had lower	**Comments:** For 13 models bonferroni correction was used to control for type 1 errors P=.05/13= .004- used for total dementia not ad For analyses other than the 13 models a significance level of 0.05 was used. Endpoint was total dementia with AD causing 47% plus 19% mixed dementia. **Quality assessment:** *For RCTs:* 1) Baseline comparability? Partial. Some differences- see differences above

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Comparator interventions*:* Matching placebo **Number of participants enrolled:** 2947 in estrogen-alone trial 4532 in estrogen plus progestin trial **Duration of follow up:** 4.05 (1.19) **Time from risk factor assessment to final cognitive assessment:** 4.05 (1.19)	**Inclusion criteria:** Participating in WHIMS study **Exclusion criteria:** Probable dementia	**Method of assessing risk factor/exposure 2:** other – RCT **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Smoking Self report cardiovascular dx Hypertension Diabetes Prior HRT or unopposed estrogen therapy Statin use Aspirin use **Baseline cognitive status:** **Method(s) of assessing cognitive status:** DSM- IV for dementia. Plus blinded adjudicators. Other – MCI operationally defined as 10th percentile or lower on 1 or more cerad tests and a report of some fct impairment, but not	baseline 3MSE scores, more ethnically diverse, more likely to have hx of stroke or coronary heart disease and to have used hrt previously (p<.001 for all) **3) Outcome of interest #1** Classification of alzheimer's disease By treatment assignment CEE: 13 of 28 dementias were AD Placebo: 9 of 19 dementias were AD CEE+MPA: 20 of 40 dementias dx as AD Placebo: 12 of 21 dementias dx as AD. Combined HRT trials HRT 33 of 68 Placebo 21 of 40 **4) Outcome of interest #2** Classification of MCI by treatment CEE: 76 Placebo: 58 HR 1.34 (95% CI 0.97-1.60) In combined CEE and CEE + MPA trial the risks were similar HR 1.25 95% CI 0.97-1.60 **5) Outcome of interest #3** Total dementia: CEE HR 1.49 (0.83-2.66) Rate per 10,000 person-years CEE + MPA HR 2.05 (1.21-3.48) Rate per 10,000 person-years Combined 1.76 (1.19-2.60) Rate per 10,000 person-years	2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%? No 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			enough to interfere with basic adls (eating dressing grooming) from informant **Informant interview?:** Yes for individuals with cognitive impairment		
Shumaker, Legault, Rapp, et al., 2003 WHIMS	**Geographical location:** 39 WHI Centers in the US **Setting:** Clinical **Study design:** RCT **Test intervention** 1 daily tablet of .625mg of conjugated equine estorogen plus 2.5 mg of medroxyprogesterone acetate **Comparator intervention(s)** Matching placebo **Number of participants enrolled:** 4532 **Duration of follow up:** 4.05 (1.19) years **Time from risk factor**	**Age:** Range: 65 + **Sex:** [n (%)] Female: 4352 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Post menopausal Free of probable dementia Age 65 or older **Exclusion criteria:** 64 or younger Male Pre-menopausal Probable dementia	**Risk factor/exposure 1:** CEE 0.625mg + MPA 2.5 mg vs placebo **Method of assessing risk factor/exposure 1:** RCT pill count **Covariates/potential confounders adjusted for in analyses:** not varied for MCI or AD **Method(s) of assessing cognitive status:** DSM IV DSM- IV for dementia. Plus blinded adjudicators. MCI operationally defined as 10th percentile or lower on 1 or more cerad tests and a report of some fct impairment, but not enough to interfere	**1) Follow-up rate:** CEE + MPA at 5 years 408/2229= 18.3% Placebo at 5 years 479/2303= 20.8% Adherence rates were lower for each year in CEE+MPA compared to placebo (p<.001) **2) Important baseline differences:** Slightly lower prevalence of stroke (p=.01) and higher prevalence of statins (p=.02) in the CEE + MPA group. **3) Outcome of interest #1** CEE+MPA: 20 of 40 dementias dx as AD Placebo: 12 of 21 dementias dx as AD. Reported in shumaker 2004, #2491 and in evidence table for #2491 HR 2.05 (1.21-3.48) for total dementia Rate per 10,000 person-years. **4) Outcome of interest #2** MCI CEE +MPA 56 of 2229 f/u mean 3.99 (SD 1.23)	**Comments:** None **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes Slight differences listed 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%? No, not at 5 years 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment to final cognitive assessment: 4.05 (1.19) years		with basic adls (eating dressing grooming) from informant **Informant interview?:** Yes	rate/10000 person years 63 Placebo 55 of 2303 f/u mean 4.04 (SD 1.20) rate/10 000 person years 59 HR 1.07 (0.74-1.55)	
Skoog, Lithell, Hansson, et al., 2005 Study on Cognition and Prognosis in the Elderly (SCOPE)	**Geographical location:** Not specified; SCOPE was in 15 countries **Setting:** Clinical **Study design:** RCT **Test intervention :** Candesartan 8-16mg daily; other antihypertensives allowed **Comparator intervention(s):** Placebo; other antihypertensives allowed **Number of participants enrolled:** 4937 **Duration of follow up:** 3.7 yrs range 3 – 5 yrs **Time from risk factor assessment to final cognitive**	**Age:** Range: 70 – 89 years **Sex:** [n (%)] NR **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** mmse ≥ 24 **Inclusion criteria:** 70 – 89 years; Mild to moderate hypertension; MMSE score ≥ 24 **Exclusion criteria:** Secondary hypertension; Stroke; MI within 6 months; Serious concomitant diseases affecting survival; Dementia	**Risk factor/exposure 1:** antihypertensive candesarten (ace i) **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** country and Baseline cognitive status **Method(s) of assessing cognitive status:** change in mmse as continuous measure and as categorical outcomes (>=4 point decline) **Informant interview?:** No	**1) Follow-up rate:** can't tell. **2) Important baseline differences:** candesartin vs placebo "similar", those with "low" mmse had lower education, were older, more women, more hx cva, more dm, **3) Outcome of interest #1** the risk of cognitive decline did not differ between candesartan and placebo (rates not given for participants by intervention). Subgroup analysis: Low cognitive function (baseline MMSE 24-28): candesartan 6.1% vs. placebo 7.0%; p=NS) High cognitive function (baseline MMSE 28-30): candesartan 3.5% vs. placebo 3.7%; p=NS) **4) Outcome of interest #2** In the low mmse group, the mmse score declined less with candesartan than with placebo (mean difference 0.49, (95% CI 0.02 – 0.97) In the high cognitive function group, there was no difference in rate of MMSE decline (-0.8 candesartan vs.	**Comments:** We were unable to confirm the criteria used for their dementia dx. "Information on sxs in pts who developed suspected dementia or signif cognitive decline was reported on a special form" For scope overall, hctz was added to 49% of candesartan group and 66% of the control group. Target BP <160/90 **Quality Assessment:** *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Partial 3) Subjects/providers blind? Can't Tell 4) Outcome assessors blind? Can't Tell 5) Incomplete data adequately addressed? No 6) Differential dropout rate < 10%? Can't Tell 7) Overall dropout rate < 30%? Can't Tell 8) Conflict of interest reported and insignificant? Can't Tell 9) Randomization adequate? Yes 10) Allocation concealment

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment: mean=3.7 years			-0.73 placebo, p>0.20)	adequate? Yes
Slooter, Cruts, Hofman, et al., 2004	**Geographical location:** Rotterdam **Setting:** Community **Study design** Prospective cohort **Number of participants enrolled:** 6,852 **Duration of follow up:** 4 years **Time from risk factor assessment to final cognitive assessment:** Not stated when APOE genotyping was done	**Age:** Mean (SD): Reported by genotype with means ranging from 67.9 to 72.2 **Sex:** [n (%)] Female: 59.8 Male: 40.2 **Race/ethnicity:** [n (%)] 100% Caucasian **Baseline cognitive status:** Dementia present in 351 subjects at baseline= 5.1% population **Inclusion criteria:** Age >55 living in Rotterdam **Exclusion criteria:** NR	**Risk factor/exposure 1:** APOE genotype **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM III-R **Informant interview?:** Yes	**1) Follow-up rate:** 6852/7983= 85.8% 1131 (14%) of cohort could not be genotyped. **2) Important baseline differences:** Increased prevalent dementia (12 vs 3%) and younger age (67.9 (8.0) vs 69.9 (9.4))in 4/4 compared to 3/3 **3) Outcome of interest #1** Relative Risk of AD by genotype AD n = 256 RR (95% CI) p values compared to E3/3 E2/2 = 1.0 (0.2 to 3.9) E2/3 = 0.5 (0.3 to 0.9) p<.05 E2/4 = 2.4 (1.3 to 4.4) p<.005 E3/3 = 1 (reference) E3/4 = 2.2 (1.6 to 2.9) p<.005 E4/4 = 7.0 (4.1 to 11.9) p<.005	**Comments:** 5.1% of subjects had prevalent dementia at baseline, but subjects with prevalent dementia at baseline were excluded from analysis of the association of APOE on dementia **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Smith, Clark, Nutt, et al., 1999	**Geographical location:** United Kingdom	**Age:** Mean (SD): Placebo: 66.9 (0.56) Vitamin: 66.8(0.48)	**Risk factor/exposure 1:** vitamin	**1) Follow-up rate:** Not specifically reported but appears to be 185/205 [JIA SR reported that placebo group 16.% % dropped out	**Comments:** None **Quality assessment:**

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Setting: Community – recruited with advertisements **Study design:** RCT **Test intervention:** 2 mg beta carotene, 400 mg alpha - tocopherol and 500 mg/ascorbic acid daily **Comparator intervention(s):** placebo **Number of participants enrolled:** 205 **Duration of follow up:** 1 year **Time from risk factor assessment to final cognitive assessment:** 1 year	**Sex:** [n (%)] Female: 110 (54) Male: 95 (46) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented (at least not profoundly demented) **Inclusion criteria:** The inclusion criteria were: aged between 60 and 80 years and within two standard deviations of the normal weight for height, age and sex; no history or evidence of significant disease or mental illness; able and willing to give informed consent; capable of taking 80±120 per cent of the prescribed number of capsules during the run-in period (subjects were given 70 placebo capsules and told to take two daily for a period of 4 weeks. Compliance was considered acceptable if they took between 45 and 67 capsules).	**Method of assessing risk factor/exposure 1:** Self-report Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Vegetable/fruit consumption; alcohol consumption; smoking; somatic symptoms; levels of other anti-oxidants **Method(s) of assessing cognitive status:** Other – change on cognitive measures **Informant interview?:** No	and vitamin group 2.1 dropped out.] **2) Important baseline differences:** No significant differences **3) Outcome of interest #1** Number of significant findings on all cognitive measures did not exceed the number one would expect to find by chance (4/117 significant). Did not give significance level.	*For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Can't Tell 4) Outcome assessors blind? Can't Tell 5) Incomplete data adequately addressed? Can't Tell 6) Differential dropout rate < 10%? No 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Can't Tell 9) Randomization adequate? Can't Tell 10) Allocation concealment adequate? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		Exclusion criteria: Exclusion criteria were: current medication likely to influence the outcome measures; use of vitamin supplements in the preceding 3 months; evidence or history of regular or chronic drug abuse including alcohol; significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, neurological disease or abnormality; malabsorption syndrome; psychiatric disorder; subjects unable or unwilling to give informed consent; disorders which would interfere with the understanding or compliance with the study, hypersensitivity to any of constituents in the active treatment; MMSE score < 18; participation in another drug clinical trial within the previous 6 months; subjects from whom blood samples could not be obtained.			
Solfrizzi, D'Introno, Colacicco,	**Geographical location:** 8 Italian municipalities	**Age:** Mean (SD): 73.4 (5.6)	**Risk factor/exposure 1:** alcohol	**1) Follow-up rate:** 2963/4521 completed baseline (226 demented, 1171 ref cognitive tests,	**Comments:** Q2 only

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
et al., 2007 Italian Longitudinal Study on Aging (ILSA)	**Setting:** Community-includes residents of institutions **Study design:** Prospective cohort **Number of participants enrolled:** 1566 analytical sample **Duration of follow up:** 3.5 yr **Time from risk factor assessment to final cognitive assessment:** 3.5 yr	**Sex:** Female: 1374 (43.6%) Male: 1589 (56.4) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented but some had MCI **Inclusion criteria:** Aged 65 to 84 residing in 8 Italian municipalities **Exclusion criteria:** Dementia at baseline (excluded from present analyses)	**Method of assessing risk factor/exposure 1:** Self-report - amount of beer, wine, 'shots of spirits' consumed in previous year. Also asked about life long history of alcohol use. **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Smoking CAD Diabetes Hypertension Stroke cholesterol **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM Other – MCI defined by modified Petersen criteria **Informant interview?:** Yes	161 education unknown) 1445/2963 with baseline normal cognition completed follow-up 121/139 with MCI completed follow-up **2) Important baseline differences:** Statistical comparisons not reported **3) Outcome of interest #1** No significant associations between any levels of drinking and the incidence of MCI in non–cognitively impaired individuals vs abstainers. **4) Outcome of interest #2** MCI moderate drinkers (<1 drink/day) had a lower rate of progression to dementia than abstainers (hazard ratio [HR] 0.15; 95% CI 0.03 to 0.78) MCI moderate drinkers (<1 drink/day) of wine had a lower rate of progression to dementia than abstainers (HR 0.15; 95% CI 0.03 to 0.77). No significant association between higher levels of drinking (≥1 drink/day) and rate of progression to dementia in patients with MCI vs abstainers.	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? No 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Solfrizzi, Panza,	**Geographical location:**	**Age:** Range: 65 - 84	**Risk factor/exposure 1:**	**1) Follow-up rate:** 2963/ 4134 (the difference in these	**Comments:** None

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Colacicco, et al., 2004 Italian Longitudinal Study on Aging (ILSA)	8 Italian Municipalities: Genoa, Segrate (Milan), Selvazzano-Rubano (Padua), Impruneta (Florence), Fermo (Ascoli-Piceno), Naples, Casamassima (Bari), and Catania **Setting:** Community (but also includes nursing homes). **Study design:** Prospective cohort **Number of participants enrolled:** 2963 (they seem to have used different pools of subjects for different risk factors (e.g., some risk factors required laboratory work and thus had a smaller n) **Duration of follow up:** 3.5 yrs **Time from risk factor assessment to final cognitive assessment:** 3.5 yr	**Sex:** [n (%)] Female: 1373 (46.3%) Male: 1590 (53.7%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Normal MCI **Inclusion criteria:** Independent or institutionalized; on electoral rolls of stated municipalities; each site was stratified by gender and age **Exclusion criteria:** Brain tumors, cerebrovascular malformations, psychosis, epilepsy, MS, stage III syphilis, dementia and any active neuropsychiatric condition producing disability, subjects taking neuroleptics	smoking **Method of assessing risk factor/exposure 1:** Smoking by self-report **Risk factor/exposure 2:** Diabetes **Method of assessing risk factor/exposure 2:** self report or hyperglycemia on blood work and confirmed with medical records and subject's physician. **Risk factor/exposure 3:** HTN **Method of assessing risk factor/exposure 3:** self report, direct measurement, medical records **Covariates/potential confounders adjusted for in analyses:** Age Educational level Total cholesterol HTN Coronary artery	numbers are those who were excluded from study because they refused cognitive screening test). It is not the best measure of follow-up rate but only one provided. **2) Important baseline differences:** NR **3) Outcome of interest #1** Number of pack-years of smoking not associated with risk of incident MCI in multi-variate models **4) Outcome of interest #2** Ever vs never smoking did not alter risk of progression from MCI to dementia	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Partial 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Partial

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			disease **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM Other – variation of Petersen's criteria for MCI **Informant interview?:** Yes		
Staehelin, Perrig-Chiello, Mitrache, et al., 1999 Basel IDA	**Geographical location:** Basel, Switzerland **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 332 **Duration of follow up:** 2 years **Time from risk factor assessment to final cognitive assessment:** APOE genotype obtained at second assessment	**Age:** Mean (SD): young old 71.43 years (115 men and 72 women Old-old mean age 82.58 years (112 men and 33 women) **Sex:** [n (%)] Female: 31.6 Male: 68.4 **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** A randomly selected subsample of the Basel IDA **Exclusion criteria:** NR	**Risk factor/exposure 1:** APOE **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Lipids Smoking **Method(s) of assessing cognitive status:** Other – computerized test for free recall (FR), and information processing speed.	**1) Follow-up rate:** 442 subjects randomly identified. 332 have full data. 110 dropped out due to death, ill health, changed mind about participating. 332/442= 75.1% **2) Important baseline differences:** Subjects who completed study are likely to be in better health than those who did not complete study. **3) Outcome of interest #1** No significant changes in any outcome measure (FR, RT and WVT) after 2 years. **4) Outcome of interest #2** At baseline: Adjusting for age and education: E4/4 and E3/4 performed lowest in FR, RT and WVT compared to E3/3 or carriers of one or two E2 alleles (FR P=.05; RT P=.009; WVLT P<.05)	**Comments:** Study is limited by small sample size and 2 year follow-up. Subjects with E4 allele performed more poorly at baseline on FR, RT and WVLT. No significant change in any outcome measure was found over two year follow-up. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Recall consists of describing all the elements of a scene that the subject can remember. Reaction time (RT) was assessed by responding to flashing suns on screen. WAIS-R vocabulary test (WVT)- define 32 words **Informant interview?:** No		7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Stott, Falconer, Kerr, et al., 2008 PROSPER (Prospective Study of Pravastatin in the Elderly Risk)	**Geographical location:** Ireland, the Netherlands, and Scotland **Setting:** Community-based (2nd-dary analyses of RCT data) **Study design:** Prospective cohort approach for secondary analyses of RCT **Number of participants enrolled:** 5804 **Duration of follow up:** Mean = 3.2 yr	**Age:** Provided by 3 levels of exposure and gender. Means ranged from 74.7 – 75.8 (sd ranged 3.2-3.4) **Sex:** Female: 3000 (51.7%) Male: 2804 (48.3%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented – (assume most were non-demented because a score of $\geq$ 24 on the MMSE was required for inclusion) **Inclusion criteria:**	**Risk factor/exposure 1:** Alcohol **Method of assessing risk factor/exposure 1:** Self-report – usual intake in units per week during previous month **Covariates/potential confounders adjusted for in analyses:** Age Country Educational level Baseline cognitive status Smoking status BMI Weight	**1) Follow-up rate:** NR **2) Important baseline differences:** Compared to nondrinkers, drinkers were slightly younger, had more yrs of education, more likely to smoke, less likely to have history of vascular disease or diabetes, were taller, had lower BMI, had higher HDL-C and lower triglycerides. Greater proportion of drinkers in the Netherlands than in Scotland or Ireland. **3) Outcome of interest #1** Rate of cognitive decline was similar for drinkers and nondrinkers for all cognitive domains, except the MMSE, which declined significantly less in female drinkers compared to nondrinkers (attenuated rate of decline = 0.05 MMSE units per annum, p=0.001)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Time from risk factor assessment to final cognitive assessment: Mean = 3.2 yr	Participant in PROSPER RCT, aged 70-82 with vascular risk factors or vascular disease, baseline MMSE ≥24 points **Exclusion criteria:** None except as covered by inclusion criteria.	Incident stroke History of vascular disease Test version **Method(s) of assessing cognitive status:** Other – longitudinal performance on MMSE, Stroop Color-Word test, Letter-Digit Coding test, Picture-Word Recall test. **Informant interview?:** No		10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Sturman, de Leon, Bienias, et al., 2008 CHAP	**Geographical location:** Chicago (south side), US. **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3,885 out of 6185 participants who were originally enrolled. **Duration of follow up:** 6 Yrs **Time from risk factor assessment to final**	**Age:** Mean (SD): 73.8 Range: 65- 85+ **Sex:** [n (%)] Female: 2369 (60.97%) Male: 1516 (39.02%) **Race/ethnicity:** [n (%)] Black : 2371 (61%) Non-Black: 1514 (39%) **Baseline cognitive status:** Per the methods papers, detailed cognitive testing done on all. However, AD not mentioned as exclusion criteria in this study. In further	**Risk factor/exposure 1:** BMI (Body Mass Index) **Method of assessing risk factor/exposure 1:** Direct measurement **Risk factor/exposure 2:** Chronic medical conditions including hypertension, heart disease, diabetes and stroke. **Method of assessing risk factor/exposure 2:** Self-report Direct measurement	**1) Follow-up rate:** 63.09% (3885 out of 6158 residents) 569 -missing global cognitive function scores at baseline or had only one global cognitive measurement, 1,139 died before the first follow-up, and 477 had no information on weight or height at baseline 13 participants had Body mass index (BMI kg/m2) outside a range of15 and 50 **2) Important baseline differences:** Unable to determine specifically. From text: Individuals with high BMIs were more likely to be young, female and black with higher incidences of chronic illnesses. **3) Outcome of interest #1** Association of categories of body mass index (BMI) (kg/m2) relative to	**Comments:** The main sample consists of participants with all levels of cognitive performance. From the methods papers, 543 patients were classified as intermediate or poor cognitive functioning out of which 152 patients had confirmed AD. They were not excluded. However, they do make an effort to exclude those whose MMSE is less than 24 in one analysis. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	cognitive assessment: 6 Yrs	analysis of the initial model, participants whose MMSE was less than 24 were excluded. **Inclusion criteria:** Resident of three neighborhoods in Chicago: Morgan Park, Beverly, and Washington Heights **Exclusion criteria:** Body mass index (BMI kg/m2) outside a range of15 and 50	Medication records. **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Hypertension Heart disease, Diabetes and Stroke **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM ICD Other **Informant interview?:** No	normal weight with global cognitive scores over time after adjusting for age (years, centered at 75), sex, education (years, centered at 12 years), and the time on study (years since baseline) Underweight x time for Black participants: Coefficient 0.0164 p value 0.379 Underweight x time for non black participants: Coefficient 0.0512 p value 0.011 Overweight x time for Black participants: Coefficient 0.0012 p value 0.849 Overweight x time for Non Black participants: Coefficient 0.0102 p value 0.191 Obese x time for Black participants: Coefficient 0.0072 p value 0.275 Overweight x time for Non Black participants: Coefficient 0.0119 p value 0.234 [Note: above sample had participants with all levels of cognitive functioning) **4) Outcome of interest #2** Association of body mass index (BMI) (kg/m2) with global cognitive scores over time among participants with Mini-Mental State Examination (MMSE) score greater than or equal to 24:	4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? No 8) Adequate follow-up period? Yes 9) Completeness of follow-up? No 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				BMI X time for black participants: Coefficient 0.0003 p value 0.415 BMI X time for Non Black participants: Coefficient 0.0008 p value 0.086	
Swan, DeCarli, Miller, et al., 1998 NHLB Institute Twin Study	**Geographical location:** USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1028 at baseline for larger study; 392 available for analysis in this sub-study **Duration of follow up:** baseline 1969-1972, cv followups 79-80 and 85-86 (and first cognitive) and 95-97 **Time from risk factor assessment to final cognitive assessment:** Bp's checked waves 1-3, cognitive 85-86 and 95-97	**Age:** Range: 68 – 79 years **Sex:** Male: 100% **Race/ethnicity:** White 100% **Baseline cognitive status:** doesn't really say, but baseline age was 46-47 **Inclusion criteria:** Participating in the NHLBI Twin Study **Exclusion criteria:** Ineligible or unwilling to undergo MR imaging	**Risk factor/exposure 1:** htn **Method of assessing risk factor/exposure 1:** Direct measurement Mean of bps taken lying, sitting, standing then first three waves averaged **Covariates/potential confounders adjusted for in analyses:** Age, stroke hx, Educational level **Method(s) of assessing cognitive status:** change in test scores **Informant interview?:** No	**1) Follow-up rate:** maybe 317/392, 70.9%, not clear **2) Important baseline differences:** increasing levels of midlife sbp were associ with age, incid cvd, chd and prevalent pad, antihypertensives associ with sbp **3) Outcome of interest #1** Subjects with high midlife sbp experienced a greater decline than those with low sbp (<120), 10 year change mmse $\pm$sem low sbp 0.04 $\pm$ 0.28, high sbp -0.66 $\pm$ 0.36 dss test -1.55 $\pm$ 0.69 for low sbp, -5.03 $\pm$ 0.84 for high sbp	**Comments:** largely the same group as Carmelli **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Szekely, Breitner, Fitzpatrick, et al., 2008 Cardiovascular Health Cognition Study (CHCS – sub-group of CHS)	**Geographical location:** Sacramento, County, CA Washington County, MD Forsyth County, NC Allegheny County, PA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3229 **Duration of follow up:** annually up to 10 years **Time from risk factor assessment to final cognitive assessment:** both assessment and rf done 1992-4 and annually	**Age:** Range: ≤ 75 yo 1631 (51%) > 75 yo 1598 (49%) **Sex:** [n (%)] Female: 1931 (59.8%) Male: 1298 (40.2%) **Race/ethnicity:** [n (%)] African American 471 (14.6%) White 2743 (84.9%) Other 15 (0.5%) **Baseline cognitive status:** Not demented **Inclusion criteria:** Participation in Cardiovascular Health Cognition Study; ≥ 65 yo; free of dementia @ baseline; info available for Rx and OTC medications **Exclusion criteria:** NR	**Risk factor/exposure 1:** nsaids **Method of assessing risk factor/exposure 1:** examined pill bottles **Covariates/potential confounders adjusted for in analyses:** Age Sex, Education, E4, baseline 3MS Educational level Baseline cognitive status **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes- the majority of the living had an informant; multiple approaches used for living and deceased individuals	**1) Follow-up rate:** This includes 3,229 subjects who were not demented in 1992-1994 visit. Not clear how many were followed for how long. **2) Important baseline differences:** nsaid users: more women, younger, more arthritis. **3) Outcome of interest #1** HR with nsaids 0.62 (0.44-0.88) **4) Outcome of interest #2** no 'greater reduction' (assume means still was a significant reduction) in HR with lagging of exposure, longer use, higher doses – These are the results we need to use, but actual HR not given for these **5) Outcome of interest #3** possibly only reduced if e4 POSITIVE HR 0.34 (0.18-0.65)	**Comments:** The results we used are those that were limited to exposure being at least 1-2 years prior to outcome. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Partial
Szwast, Hendrie, Lane, et al., 2007 Indianapolis Ibadan	**Geographical location:** Indianapolis, IN **Setting:** Community	**Age:** Mean (SD): 77.3 (5.3) **Sex:** Female: 791 (69.3%) Male: 350 (30.7%)	**Risk factor/exposure 1:** Statin use (simvastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, lovastatin), medical	**1) Follow-up rate:** 1146 of 1808 with ApoE data (63.1%) **2) Important baseline differences:** The statin and non statin users differed significantly in the following:	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Dementia Project	**Study design:** Prospective cohort **Number of participants enrolled:** 2519 **Duration of follow up:** 3 yrs **Time from risk factor assessment to final cognitive assessment:** 0 to 3 yrs	**Race/ethnicity:** African American 1146 (100%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** 1992 sample: African American; ≥ 65 yo 2001 sample: African American; ≥ 70 yo; Medicare beneficiary **Exclusion criteria:** No ApoE results at baseline; dementia	history, smoking, alcohol use, social involvement **Method of assessing risk factor/exposure 1:** Self-report Direct measurement – for statins: medication bottles or printed lists from pt's Dr at baseline **Risk factor/exposure 2:** BP, height, weight, ApoE, lipids **Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age , sex, years of educations, statin use at baseline, Any Apoe E4 allele **Method(s) of assessing cognitive status:** Other – Community Screening Interview for Dementia (0-34 with higher scores indicating better cognitive function)	Age at baseline, BMI at baseline, h/o hypertension, h/o stroke, h/o diabetes, h/o heart disease, cholesterol level >300 mg/dl, LDL-C >130, use of NSAIDS, use of antipatelet medication/ asprin. Baseline: 284 on statin only, 3 on statin + other lipid lowering agent Statin use at baseline 3) Continuous outcome [for each such outcome, please report the following information wherever possible for the exposed/intervention group and the unexposed/control group: - N, mean value and SD at baseline - N, mean value, and SD at follow up, and/or the N and mean change and SD of the change. If these values are not given, abstract whatever *is* reported.] 287 on statins, 854 non-statin 1. Analysis of covariance, adjusting for age, gender, education, ApoE e4 allele. Cognitive decline = CSI-D scores at baseline minus 3-year f/u score standardized to effect sizes. Parameter estimate (Value > 0 indicates cognitive decline), SE, p value Female: 0.02, 0.06, p=0.7489 Education(years): -0.02, 0.01, p=0.1668 ApoEe4: 0.15, 0.06, p=0.0149 Baseline statin: -0.16, 0.07, p=0.0177	2) Selection minimizes baseline differences in prognostic factors? Partial 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Can't Tell 9) Completeness of follow-up? No 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Informant interview?: Yes- They used the CAMDEX	Adjustment for baseline cognitive score, statins associated with less cognitive decline (only p value given, p=0.0046) 2. Analysis of covariance, adjusting for age, gender, education, ApoE e4 allele. Cognitive decline = CSI-D scores at baseline minus f/u score standardized to effect sizes. Parameter estimate (Value > 0 indicates cognitive decline), SE, p value Female: 0.03, 0.06, p=0.6076 Education(years): -0.02, 0.01, p=0.1708 ApoEe4: 0.16, 0.06, p=0.0115 Baseline statin only: -0.28, 0.12, p=0.0217 Statin at 3 year f/u only: 0.04, 0.10, p=0.6765 Statin at baseline and f/u: -0.12, 0.08, p=0.1258	

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Tang, Cross, Andrews, et al., 2001 WHICAP	**Geographical location:** Manhattan, NY, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1788 **Duration of follow up:** Mean 4.3 yrs SD1.4 (Caribbean Hispanic; 1.5 white and AA) **Time from risk factor assessment to final cognitive assessment:** Mean 4.3 yrs SD1.4 (Caribbean Hispanic; 1.5 white and AA)	**Age:** Mean (SD): AA 75.8 (6.2); Caribbean Hispanic 74.9 (5.8); white 76.9 (7.2) **Sex:** [n (%)] Female: 224 (12.5%) Male: 1564 (87.5%) **Race/ethnicity:** [n (%)] Caribbean Hispanic: 42.5% AA: 34.1% White: 23.4% **Baseline cognitive status:** Non-demented **Inclusion criteria:** Random sample from 3 contiguous zip codes within Washington Heights, NY, aged ≥ 65 yrs old Current analyses included subset with baseline and longitudinal follow-up **Exclusion criteria:** Dementia	**Risk factor/exposure 1:** Diabetes mellitus **Method of assessing risk factor/exposure 1:** medical history, medication **Risk factor/exposure 2:** Stroke, heart disease, hypertension **Method of assessing risk factor/exposure 2:** Self-report Medical history Other –use of medication **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level APOE Diabetes BMI Hypertension Heart disease Stroke **Method(s) of assessing cognitive**	**1) Follow-up rate:** 1788/2126 =84.1% **2) Important baseline differences:** Whites were older (p=.001) and had more years of education (p=.001) than AA or Caribbean Hispanics. AA had more education than Caribbean Hispanics (p=.001). AA and Caribbean Hispanics had more diabetes than whites (p=.01). Heart disease was more frequent in Caribbean Hispanics than AAs (p=.001). **3) Outcome of interest #1** HR developing possible or probable AD in participants with diabetes 1.6 (95% CI 1.1-2.3) (p ≤ 0.01) **4) Outcome of interest #2** Stroke HR 0.9 (95% CI 0.5-1.6) **5) Outcome of interest #3** Hypertension HR 1.4 (95% CI 0.9-1.9)	**Comments:** Question 1 Diabetes mellitus was associated with a significantly increased risk of incident AD (probable or possible in this multi-racial, multi-ethnic population. Hypertension, stroke and heart disease were not significantly associated with incident possible or probable AD. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			status: NINCDS-ADRDA DSM Other – cognitive change within cognitive domain. Used analytical method that controls for baseline score (tests combined based on factors analyses) **Informant interview?:** No		
Tervo, Kivipelto, Hanninen, et al., 2004	**Geographical location:** Kuopio, Finland **Setting:** Community Other-nursing facilities **Study design:** Prospective cohort **Number of participants enrolled:** Random sample screened: 1,150; 747 enrolled subjects **Duration of follow up:** 3.26 +/- 0.70 yrs **Time from risk factor assessment to final cognitive assessment:** 3.25 +/- 0.72 yrs	**Age:** Range: 60-76 yrs **Sex** Female: 454 (61%) Male: 293 (39%) **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** 60 yrs and older, non-demented; no evidence MCI **Exclusion criteria:** NR	**Risk factor/exposure 1:** Education, years **Method of assessing risk factor/exposure 1** Self-report **Risk factor/exposure 2:** ApoE4 allele **Method of assessing risk factor/exposure 2** Direct measurement **Risk factor/exposure 3:** Diabetes mellitus (included diet, tablet or insulin-treated) **Method of assessing risk factor/exposure 3** Self report	**1) Follow-up rate:** Random sample of 1150 subjects. 806 evaluated. 747 eligible. F/u: 550/747(77.7%) **2) Important baseline differences:** NA **3) Outcome of interest #1—Education** OR (95% CI) 0.80 (0.71-0.90) **4) Outcome of interest #2--APOE** OR (95% CI) 2.23(1.23-4.05) **5) Outcome of interest #3--Diabetes** OR (95% CI) 1.55(0.58-4.19**)** **6) Outcome of interest #4—High blood pressure (DBP≥95 or**	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				SBP≥160) OR (95% CI) 0.91(0.49-1.69) **7) Outcome of interest #5—Medicated HTN** OR (95% CI) 1.61(0.87-2.99) Results: 66 subjects (8.8%) had converted to MCI. The global incidence rate of MCI was 25.94/1,000 person-years. Persons with ApoE4 allele and medicated hypertension were more likely to convert to MCI. High education is a protective factor for MCI	11) Analytic methods appropriate? Yes
			Risk factor/exposure 4: Elevated blood pressure: HTN=SBP 160 mm Hg or greater or DBP 95 mm Hg or greater. **Method of assessing risk factor/exposure 4** Direct measurement **Risk factor/exposure 5**: Medicated hypertension **Method of assessing risk factor/exposure 5** Self report **Covariates/potential confounders adjusted for in analyses** Age Race Sex Educational level Baseline cognitive status **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM-IV Other –CERAD; Clinical Dementia Rating (CDR):MCI		

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			diagnosed if score of 0.5 and if subject scored 1.5 SD below average on at least one memory test. **Informant interview?:** No		
Thal, Ferris, Kirby, et al., 2005	**Geographical location:** 46 US sites **Setting:** Other – clinical and community: combination of patients identified by investigators and volunteers responding to an ad about RCT – **Study design:** RCT **Test intervention:** Rofecoxib 25 mg **Comparator intervention(s):** placebo **Number of participants enrolled:** 1457 **Duration of follow up:** 115 weeks rofecoxib, 130 weeks placebo	**Age:** Mean (SD): Placebo = 74.8 (6.0) Drug = 75.1 (6.0) **Sex:** [n (%)] Female: 477 (32.7%) Male: 980 (67.3%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** MCI **Inclusion criteria:** ≥ 65 yo; at least 8 grades of education; had a reliable informant who could accompany them to each visit; pt or informant reported memory problem; memory has declined in last yr; MMSE ≥ 24; CDR global score = 0.5 with memory domain score ≥ 0.5; BDRS total score ≤ 3.5 with	**Risk factor/exposure 1:** nsaid **Method of assessing risk factor/exposure:** rct rofecoxib and placebo **Covariates/potential confounders adjusted for in analyses:** treatment region, mmse strata (24-26 or >26) **Method(s) of assessing cognitive status:** NINCDS-ADRDA Other – Dementia determined by CDR ≥ 1 **Informant interview?:** Yes	**1) Follow-up rate:** placebo 45% dc'd, 41% finished rofecoxib 45% dc'd, 40% finished **2) Important baseline differences:** not apparent **3) Outcome of interest #1** increased HR for AD with rofecoxib 1.46 (1.09-1.94) but a minority finished on drug, and secondary measures did not confirm increased risk (ADAS-Cog, SRT, MMSE, BDRS, CDR sum of boxes)	**Comments:** Minority finished study (which was terminated early) on drug **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? No 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%? No 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Time from risk factor assessment to final cognitive assessment: q4mos:cdr, mmse,srt, q12mos ADAS-Cog Time from 1st to last cognitive assessment = 48 mos	no part 1 item score > 0.5; AVLT total score ≤37 **Exclusion criteria:** Dementia; inadequate motor or sensory capacities to comply with testing; a modified Hachinski Ischemic Scale score > 4; Hamilton Depression Scale (17-item version) score > 13; history of angina or CHF with symptoms that occurred at rest; uncontrolled HTN; history within past yr of MI; coronary artery bypass, angioplasty, or stent placement; history within past 2 yrs of stroke, multiple lacunar infarcts, or transient ischemic events; history within past 3 months of GI bleeding; and expected therapeutic need for chronic NSAID or estrogen replacement therapy during the study; pts taking NSAIDS on a chronic basis for 2 mos prior to study; estrogen replacement therapy (excluding topical ointments) withint 2 mos of study;			

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		cholinesterase inhibitors within 1 mo of study			
Tierney, Oh, Moineddin, et al., 2009	**Geographical location:** Greater Toronto area **Setting:** Community **Study design** RCT **Test intervention** *(RCTs only)***:** Per week 1 mg 17-β estradiol for 4 days, then combo with 0.35 norethindrone for 3 days **Comparator intervention(s)** *(RCTs only)***:** placebo **Number of participants enrolled:** 142 **Duration of follow up:** 2 year trial **Time from risk factor assessment to final cognitive assessment:** NR	**Age:** Mean (SD): 74.8 (6.9) **Sex:** [n (%)] Female: 142 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] White 132 (93.0 %) Black 6 (4.2%) Asian 4 (2.8%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age ≥ 60 with last menstrual cycle ≥ 12 months before screening; were fluent in English; could read normal print and hear normal speech. **Exclusion criteria:** Met criteria for dementia, or had a clinical history of a neurological systemic or psychiatric condition that would affect cognition; women with conditions that were considered at the time of enrollment to be	**Risk factor/exposure 1:** estrogen/progesterone hormone therapy **Method of assessing risk factor/exposure 1:** meds administered **Covariates/potential confounders adjusted for in analyses:** Age, education, apoE, prior hormone use **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM used to dx dementia per methods but outcome here is cvlt recall **Informant interview?:** No	**1) Follow-up rate:** in active tx group: 70 randomized, 4 dropped out, 1 death, 18 dc'd meds at yr 1, 2 dropped out, 1 died, 8 dc'd meds at yr 2. In the placebo group, 72 randomized, 4 dropped out and 1 died and 12 dc'd tx at yr 1. In yr 2, 1 refused, 1 died, 4 self dc'd **2) Important baseline differences:** More apoe4 carriers in placebo group. More prior ht use in tx group. **3) Outcome of interest #1** Group differences on the cvlt short delay verbal recall were not significant at year 1 or 2 **4) Outcome of interest #2** For the subgroup scoring average or above at baseline (>7), those on HT had less decline at yr 1 and yr 2 as compared to placebo (p=.007 and p=0.01) **5) Outcome of interest #3** no treatment effect for those scoring below average.	**Comments:** Question 5 – no cat Dx Primary outcome is 'short delayed' recall on CVLT. They don't give an estimate of how long their short delay is. **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Yes 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		exacerbated by estrogen, including history of breast or endometrial cancer; history of myocardial infarction (MI), coronary artery bypass graft (CABG), angioplasty or unstable angina within the past year; history of congestive heart failure (CHF) (NYHA Class III or IV); or history of thromboembolic event withint the past 6 months; women taking donepezil, galantamine, rivastigmine, hydergine, tamoxifen, or raloxifene, or had used any mode or dose of HT within the past 2 years; women who met neuropsychological criteria for dementia; women who had an identifiable cause of memory disorder (e.g., stroke) or were considered to meet criteria for dementia.			
Tyas, Salazar, Snowdon, et al., 2007	**Geographical location:** United States **Setting:**	**Age:** Mean (SD): 84.3 (5.0) **Sex:** Female: 470 (100%)	**Risk factor/exposure 1:** Education 1) ≤ High school	**1) Follow-up rate:** 1031 initially eligible. 678 (66%) agreed to participate. Exclusions: missing examinations	**Comments:** A variety of transitions of cognitive decline assessed. **Quality assessment:**

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
NUN study	Other – Nuns **Study design:** Prospective cohort **Number of participants enrolled:** 1031 initially eligible, 678 agreed to participate, 470 had complete data. **Duration of follow up:** NR. Annual exams from 1991-2002, so range is probably 1-11 years **Time from risk factor assessment to final cognitive assessment:** NR. Annual exams from 1991-2002, so range is probably 1-11 years	Male: 0 (0%) **Race/ethnicity:** NR **Baseline cognitive status:** Normal Non-demented MCI CIND AAMI **Inclusion criteria:** Members of the School Sisters of Notre Dame born before 1917 and living in certain regions of the US. Aged ≥75 yrs. **Exclusion criteria:** NR	2) Undergrad degree 3) Grad degree (reference) **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2:** APOE **Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Education APOE Prior cognitive state **Method(s) of assessing cognitive status:** Cognitive test in the Consortium to Establish a Registry for Alzheimer's Disease **Informant interview?:** No	(n=58), missing APOE data (n=35), dementia at baseline (n=115). Analytic sample: 470/678 (69%) Of the 470, 192 provided data on 6 transitions and all 7 annual exams. **2) Important baseline differences:** NA **3) Outcome of interest #1** Transitions/outcomes: 1) intact cognition 2) MCI 3) global impairment 4) death Total of 1905 transitions. From MCI to global impairment: n=110 (11.6%) From MCI to dementia: n=71 (7.5%) **4) Outcome of interest #2** Age, education, and APOE were all significant predictors of transition from intact cognition to mild cognitive impairment. Similar pattern for transition from intact cognition to global impairment. **5) Outcome of interest #3** Transition from intact to MCI, OR (95% CI): 1) Age 1.06 (1.03, 1.09) 2) Education (grad degree as ref.) --≤high school 2.36 (1.26, 4.42) --undergrad 1.53 (1.17, 2.00) 3) APOE present 1.87 (1.27, 2.73) 4) Prior cognitive state (global	*For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Can't Tell 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Partial (69%, if include exclusion for dementia at baseline) 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				impairment as ref.) --intact cognition 0.18 (0.09, 0.38) --MCI 1.82 (0.09, 3.68) <u>Transition from intact to global impairment</u>, OR (95% CI): 1) Age 1.15 (1.10, 1.20) 2) Education (grad degree as ref.) --<u><</u>high school 2.79 (1.32, 5.91) --undergrad 1.62 (1.10, 2.38) 3) APOE present 3.02 (1.87, 4.89) 4) Prior cognitive state (global impairment as ref.) --intact cognition 0.02 (0.01, 0.03) --MCI 0.11 (0.06, 0.21)	
Tzourio, Anderson, Chapman, et al., 2003 Perindopril Protection Against Recurrent Stroke Study (PROGRESS)	**Geographical location:** 172 centers in 10 countries **Setting:** Clinical **Study design:** RCT **Test intervention:** Perindopril 4mg daily +/- indapamine 2-2.5 mg daily **Comparator intervention(s):** placebo **Number of participants enrolled:** 6105	**Age:** Mean (SD): 64 (10) years **Sex:** Female: 30% Male: 70% **Race/ethnicity:** Asian: 39% Other: 61% **Baseline cognitive status:** Non-demented and cognitively impaired (15% with MMSE <25) MCI **Inclusion criteria:** H/o TIA or Stroke w/in 5 years No clear indication for , nor	**Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status **Method(s) of assessing cognitive status:** MMSE at baseline, 6- and 12-month visit, then annually Cognitive decline defined as >=3 point drop **Informant interview?:** NA	**1) Follow-up rate:** 22% discontinued use of all study tablets (active 23%; placebo 21%) Cognitive decline assessed in 5888 study participants (96.4%) **2) Important baseline differences:** No **3) Outcome of interest #1** Cognitive decline = 610 (134 with recurrent stroke, 476 w/o stroke): Active: 276/3051 (9.1%), 23/1000 person years Control: 334/3054 (11.0%), 28/1000 person years RR = 0.81 (95% CI 0.68-0.96) Sensitivity analysis defining cognitive decline as ?=2 or >=4 points did not “materially alter” the results **4) Outcome of interest #2** Change in MMSE (baseline – f/u)	**Comments:** Note – no BP criteria for entry, 48% had SBP >=160 or DBP >=90; 50% on antihypertensive medication at baseline **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Can’t Tell, probably subjects 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Partial; co-funded with Servier Pharmaceutical Company 9) Randomization adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Duration of follow up: Mean = 3.9 years **Time from risk factor assessment to final cognitive assessment:** Mean = 3.9 years	contraindication to treatment with an ACE inhibitor Tolerated and adhered to perindopril during 4-week run-in phase **Exclusion criteria:** NR		Active: 0.05 (0.05 SE) Placebo: 0.24 (0.05 SE) Difference in change (placebo – active): 0.19 (0.07 SE) less decline for active, p=0.01 **5) Outcome of interest #3** Mean difference in BP between active and control = 9/4 mm Hg	10) Allocation concealment adequate? Yes
Tzourio, Dufouil, Ducimetiere, et al., 1999 EVA	**Geographical location:** Nantes, France **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1,373 **Duration of follow up:** 4 years **Time from risk factor assessment to final cognitive assessment:** 2-4 years	**Age:** Mean (SD): 65 (3.0) **Sex:** [n (%)] Female: 807 (58.8%) Male: 566 (41.2%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Uncertain, those with cognitive impairment not specifically excluded. **Inclusion criteria:** Age 59-71 yo **Exclusion criteria:** Stroke during f/u	**Risk factor/exposure 1:** HTN : SBP ≥ 160 or DBP ≥ 95 (average of 2 measures) or taking anti-hypertensive medication **Method of assessing risk factor/exposure 1:** Self-report: medication Direct measurement: BP **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status ApoeE polymorphism, Depressive symptomatology **Method(s) of**	**1) Follow-up rate:** 1,255/1373 completed 2 yr f/u 1172/1373 completed 4 year f/u Non participants had lower MMSE at baseline (27.1 vs. 28.2) **2) Important baseline differences:** HTN associated with: male, heavy drinking, smoking and higher BMI; MMSE scores were similar **3) Outcome of interest #1** HTN: OR for cognitive decline = 2.8 (1.6 – 5.0) Sensitivity analysis using SBP ≥ 140 or DBP ≥90 to define HTN: OR for cognitive decline = 2.8 (1.1 to 2.9) **4) Outcome of interest #2** HTN and antihypertensives High BP with anti-HTN medication: OR=4.3 (2.1-8.8) High BP w/o anti-HTN medication: OR=1.9 (0.8 – 4.4) Normal BP with anti-HTN medication: OR=1.2 (0.6-2.2) Normal BP w/o -HTN medication: OR	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial, insufficient detail on selection criteria. 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			assessing cognitive status: Other – >=4 point decline on MMSE between baseline and 4 year f/u **Informant interview?:** No	1 (reference) **5) Outcome of interest #3** Anti-HTN medication at baseline: OR for cognitive decline = 1.1 (0.7 -1.7)	
Unverzagt, Kasten, Johnson, et al., 2007 Advanced Cognitive training for Independent and Vital Elderly (ACTIVE)	**Geographical location:** Birmingham Al; Detroit Mich; Boston Mass; Baltimore Md; Indianapolis In; State College Pa; **Setting:** Other – Senior Housing Community Centers Hospitals Clinics **Study design:** RCT **Test intervention:** Reasoning Training Memory Training Speed Training. **Comparator intervention(s):** No Training (Control) **Number of participants enrolled:** 2832	**Age:** Mean (SD): 73.6 (5.9) **Sex:** [n (%)] Female: 2078 (74.16%) Male: 754 (25.84%) **Race/ethnicity:** [n (%)] 26% Black **Baseline cognitive status:** MMSE ≥ 23 No self reported AD **Inclusion criteria:** NR **Exclusion criteria:** < 65 yrs of age; functional impairment (≥2ADLdisabilities); cognitive decline (MMSE score ≤22); self reported AD/stroke/ uncertain cancer; severe losses in vision, hearing, or communicative ability	**Risk factor/exposure 1:** NA **Method of assessing risk factor/exposure 1:** NA **Covariates/potential confounders adjusted for in analyses:** Cant tell. From the manuscript, it appears that they did not control for age, sex, or education. **Method(s) of assessing cognitive status:** MMSE and self report To divide the baseline sample into memory normal and memory impaired they used the AVLT test. **Informant interview?:**	**1) Follow-up rate:** 2832 randomized. 2244 analyzed at year 2. Follow up: 79% However, since they did ITT, 2802were included in the analysis. **2) Important baseline differences:** The memory impaired group was older and had lower MMSE scores. **3) Outcome of interest #1** At years 1 and 2 the memory normal group (n=2580) who received- memory training did better than controls on memory tests. Year 1 :Effect size= 0.254, p<0.001 Year 2: Effect size= .214, p<0.001 reasoning training did better than controls on reasoning tests Year 1 Effect size= 0.416, p<0.001 Year 2 Effect size= 0.262, p<0.001 speed training did better on speed processing tests Year 1 effect size= -1.238, p<0.001 Year 2 effect size= -0.886, p<0.001 (negative effect sizes indicate better performance of this groups on the	**Comments:** None **Quality assessment:** *For RCTs:* 1) Baseline comparability? Can't Tell 2) Valid AD/cognitive outcomes assessment? Can't Tell 3) Subjects/providers blind? Partial 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Can't Tell 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? No 9) Randomization adequate? Yes 10) Allocation concealment adequate? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Duration of follow up: 2 years **Time from risk factor assessment to final cognitive assessment:** 2 years	that would interfere with study participation; recent cognitive training; or unavailable during the study period	No	raw scores) **4) Outcome of interest #2** At years 1 and 2 the memory impaired group (n=193) who received- memory training did better no than controls on memory tests. reasoning training did better than controls on reasoning tests in year 2 only Year 1 Effect size= 0.208, p>0.05 Year 2 Effect size= 0.276, p<0.05 speed training did better on speed processing tests Year 1 effect size= -1.100, p<0.001 Year 2 effect size= -0.755, p<0.001	
van Gelder, Tijhuis, Kalmijn, et al., 2006 Finland, Italy, the Netherlands Elderly (FINE) Study	**Geographical location:** Finland, Italy, the Netherlands **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1383 **Duration of follow up:** 15 years **Time from risk factor**	**Age:** Range: 65 – 84 years **Sex:** Female: 0% Male: 100% **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** MMSE >24 **Inclusion criteria:** Finnish, Dutch, or Italian survivor of the Seven Countries Study	**Risk factor/exposure 1:** Marital Status **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2:** Living situation **Method of assessing risk factor/exposure 2:** Self-report **Covariates/potential**	**1) Follow-up rate:** 1363 men were recruited in 1985. Information for 1042 men in 1990. Follow up for year 2000 NR. **2) Important baseline differences:** Men who were not included in the present study were older (in 1990, mean ageof 79 years vs 76 years, p < .001), had lower education (5 years vs 7 years, p < .001), and were more likely to have a history of stroke (13% vs 5%, p < .001) compared to the men who participated. **3) Outcome of interest #1** After adjustment for age, education, country, smoking, alcohol	**Comments:** We do not know the rate of follow up. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? No 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	assessment to final cognitive assessment: 10 years.	Male **Exclusion criteria:** Female Institutionalized MMSE score ≤ 18	**confounders adjusted for in analyses:** Age Country Educational level Smoking status Alcohol Consumption Baseline cognitive status Prevalence of MI Stroke Diabetes Cancer Hypertension Physical activity Depression Functional status For the analysis of marital status, living situation was included as a covariate. **Method(s) of assessing cognitive status:** Other – MMSE **Informant interview?:** No	consumption, prevalence of myocardial infarction, stroke, diabetes and cancer, living situation, and baseline cognitive functioning, men who were married from 1985-90 had a cognitive decline of 1.1 point (95% CI 0.9–1.4) over the 10 year follow up. Men who were married in 1985 but unmarried in 1990 had a cognitive decline of additional decline of 1.0 point(95% CI 0.1–1.9) Men who were unmarried in 1985 and 1990 had an additional decline of 1.3 points (95% CI 0.5–2.1) **4) Outcome of interest #2** After adjustment of after adjustment for age, education, country, smoking, alcohol consumption, prevalence of myocardial infarction, stroke, diabetes and cancer, marital status, and baseline cognition men who lived with others in 1985 and 90 had a cognitive decline of 1.1 points (95% CI 0.8–1.4) Men who lived with others in 1985 but alone in 1990 had an additional decline of 1.1 points (95% CI¼0.2–2.0) Men who lived alone in 1985 and 1990 had an additional cognitive decline of 2.7 points (95% CI 1.7–3.7)	7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Verghese,	**Geographical**	**Age:**	**Risk factor/exposure**	**1) Follow-up rate:**	**Comments:**

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
LeValley, Derby, et al., 2006 Bronx Aging Study	**location:** NY, NY **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 488; 437 in relevant subsample **Duration of follow up:** 2713 person-years. Mean: 5.6 yrs +4.1. 21-year study period. **Time from risk factor assessment to final cognitive assessment:** Mean: 5.6 yrs +4.1. 21-year study period.	No aMCI: 79.0 +3.1 Incident aMCI: 78.9 +2.8 **Sex:** Female: No aMCI: 64.7% Incident aMCI: 58.6% Male: No aMCI: 35.3% Incident aMCI: 41.4% **Race/ethnicity:** White: No aMCI: 89.2% Incident aMCI: 89.3% **Baseline cognitive status:** Non-demented **Inclusion criteria:** English speaking, age between 75 and 85 yrs, community dwelling and <= 8 errors on Blessed Information Memory Concentration Test. **Exclusion criteria:** Prevalent aMCI. Severe visual or hearing impairment, Parkinson's disease, liver disease, alcoholism, or known terminal illness.	**1:** Leisure activities **Method of assessing risk factor/exposure 1:** Self-report 6 cognitive activities and 10 physical activities Cognitive-activity and physical-activity scales in units of activity-days per week (range: 0-42 for cognitive activity and 0-70 for physical activity). Scale scores not dichotomized. **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Chronic illnesses (Participation in other leisure activities when analyzing individual leisure activities). **Method(s) of assessing cognitive status:** "Subjects with suspected dementia	437 of 488 enrolled (89.5%) in Bronx Aging Study. **2) Important baseline differences:** NA **3) Outcome of interest #1** 58 incident cases of aMCI; 84 incident cases of dementia (43 AD, 15 mixed AD) 26 incident cases of dementia after meeting aMCI criteria (11 AD, 8 mixed AD and vascular dementia, 4 vascular, and 3 other) The 58 incident aMCI patients had lower baseline cognitive ability but not physical activity scale scores. None of the individual cognitive and physical leisure activities showed independent associations wit lower risk of aMCI in the fully adjusted models. **4) Outcome of interest #2** A 1-point increment in cognitive activity score was associated with a reduced risk of aMCI (HR, 0.949; 95% CI, 0.910-0.990), but a 1-pt increment in physical activity score was not (HR=0.970, 95% CI 0.933 to 1.008). A 1-point increment in cognitive activity score was associated with a reduced risk of aMCI or Dementia (HR, 0.946; 95% CI, 0.921-0.972), but a 1-pt increment in physical activity score was not associated	None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No. 4) Adequate description of the cohort?: Yes 5) Validated method for ascertaining exposure?: No (leisure activity) 6) Validated method for ascertaining clinical outcomes?: Partially, aMCI criteria applied retrospectively 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Partial 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			received further w/u. Triggers for w/u included: new symptoms, staff observations, Blessed test score change of 4 points or more than 8 errors, or worsening neuropsych test scores. NINCDS-ADRDA DSM-IIIR "The concept of aMCI evolved after study was launched; we adapted current aMCI criteria to diagnose cases." Criteria for aMCI: 1) no dementia 2) memory impairment: >= 3 errors on 5-item Blessed test memory phrase 3) memory symptoms 4) normal cognitive function (verbal IQ >84 and score of less than 8 on the Blessed test) 5) generally preserved activities of daily living **Informant interview?:** Yes, when available	(HR=0.985, 95% CI 0.967 to 1.008).	
Verghese, Lipton,	**Geographical location:**	**Age:** No dementia: 78.9 ±3.1	**Risk factor/exposure 1:**	**1) Follow-up rate:** 469 of 488 enrolled (96.1%).	**Comments:** None

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Katz, et al., 2003 Bronx Aging Study	NY, NY **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 469 **Duration of follow up:** 2702 person-years. Median f/u of 5.1 yrs. Mean f/u for subjects in whom dementia did not develop: 5.6 ± 4.1 . Mean f/u for subjects in whom dementia did develop: 5.9 ± 4.1. **Time from risk factor assessment to final cognitive assessment:** Median 5.1 yrs	Dementia: 79.7 ±3.1 **Sex:** Female: No dementia: 63% Dementia: 67% Male: No dementia: 37% Dementia: 33% **Race/ethnicity:** White: No dementia: 92% Dementia: 91% Other: No dementia: 8% Dementia: 9% **Baseline cognitive status:** Non-demented **Inclusion criteria:** English speaking, age between 75 and 85 yrs, community dwelling. **Exclusion criteria:** Severe visual or hearing impairment, Parkinson's disease, liver disease, alcoholism, or known terminal illness.	Frequency of leisure activities. **Method of assessing risk factor/exposure 1:** Self-report Cognitive-activity and physical-activity scales in units of activity-days per week. Scales dichotomized to "rare participation" vs. "frequent participation". 6 cognitive activities and 11 physical activities **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Medical illness Baseline Blessed test score Participation in other leisure activities. **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** No	**2) Important baseline differences:** NA **3) Outcome of interest #1** Incident dementia in 124 (61 with AD) **4) Outcome of interest #2** Reading, playing board games, playing musical instruments, and dancing were associated with reduced risk of dementia. A 1-point increment in cognitive activity score was associated with a reduced risk of dementia (HR, 0.93; 95% CI, 0.90-0.97), but a 1-pt increment in physical activity score was not (HR=1.00). Results were similar for AD and vascular dementia. HR reported for all activities in Table 2 in article.	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Partial 9) Completeness of follow-up? Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Virtanen, Singh-Manoux, Ferrie, et al., 2009 Whitehall II study	**Geographical location:** London, England **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2214 **Duration of follow up:** 5 years **Time from risk factor assessment to final cognitive assessment:** 5 years	**Age:** Mean (SD): 52.1 **Sex:** [n (%)] Female: 23% Male: 77% **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Office staff from 20 London-based Civil Servant depts. Aged 35-55 between 1985 and 1988. **Exclusion criteria:** None	**Risk factor/exposure 1:** "How many hours do you work per week in your main job including work brought home?" "How many ours do you work in an average week in your additional employment?" **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Marital status Follow-up employment status Occupational grade Income Physical health indicators Psychological stress Anxiety Sleep problems Health risk behaviors Social support Family stress Job strain **Method(s) of assessing cognitive status:**	**1) Follow-up rate:** 2214/3597 **2) Important baseline differences:** Differed by # hours worked on: sex, marital status, educational level, income, and psychological distress **3) Outcome of interest #1** Compared to those who worked ≤ 40 hrs/wk, those who worked: 41-55 hrs/wk declined more on reasoning test (mean difference (-2.23; SE = 0.37; p = 0.046) >55 hrs/wk declined more on reasoning test (mean difference -2.9; SE=0.49; p = 0.007) Test for linear trend, p = 0.036	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes, but because young cohort – not much decline 9) Completeness of follow-up? Partial 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Other – Decline from baseline to follow-up on tests of memory, reasoning, vocabulary, phonemic verbal fluency, and semantic verbal fluency **Informant interview?:** No		

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Waldstein, Giggey, Thayer, et l., 2005 Baltimore Longitudinal Study of Aging (BLSA)	**Geographical location:** USA, majority from Baltimore, MD – Washington, D.C. area **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 847 **Duration of follow up:** visits every 2.32 (0.8) yrs, mean 2.7 (1.5) visits **Time from risk factor assessment to final cognitive assessment:** Calculated average 6.26 years (mean number of visits multiplied by mean number of years between visits)	**Age:** Mean (SD): 70.6 (8.5) **Sex:** Female: 344 (41%) Male: 503 (59%) **Race/ethnicity:** White 84.2% Non-white 15.8% **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participating in the BLSA **Exclusion criteria:** Dementia Cerebrovascular disease, including stroke Renal failure	**Risk factor/exposure 1:** Hypertension **Method of assessing risk factor/exposure 1:** Direct measurement once in each arm at least 90 min post breakfast, averaged **Covariates/potential confounders adjusted for in analyses:** Age, education, alcohol smoking antihypertensives depression **Method(s) of assessing cognitive status:** change in test score **Informant interview?** No	**1) Follow-up rate:** Not reported in detail. Participants had different number of follow-up assessments **2) Important baseline differences:** NR **3) Outcome of interest #1** Only significant result was a 3-way interaction of baseline age, time interval, and quadratic systolic BP for the BVRT and the Boston Naming Test. For the BVRT, among younger individuals (age 60 at baseline), those with higher systolic BP made more errors on the BVRT than those with normal BP but improved over time (ie, practice effects). In contrast, among older individuals (age 80 at baseline), those with higher systolic BP declined in BVRT performance over time. On the Boston Naming Test, younger individuals (age 60 at baseline) with higher systolic BP performed more poorly than those with lower systolic BP across testing sessions. For older individuals (age 80 at baseline), those with higher systolic BP declined in performance over time.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Wang, Wahlin, Basun, et al., 2001 Kungsholm	**Geographical location:** Stockholm Sweden **Setting:** Community	**Age:** Range: 75-101 **Sex:** [n (%)] Female: 298 (80.54%) Male: 72 (19.46%)	**Risk factor/exposure 1:** B12 **Method of assessing risk factor/exposure**	**1) Follow-up rate:** 86 out of the 370 subjects died before the follow up period. Information on them was derived from hospital records.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
en study subset	**Study design:** Prospective cohort **Number of participants enrolled:** 668 selected from initial sample. 443 included as non demented. **Duration of follow up:** 3 years. **Time from risk factor assessment to final cognitive assessment:** 3 years	**Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Normal Non-demented **Inclusion criteria:** Born in 1912, Living in Kungsholmen area. **Exclusion criteria:** Refusing blood test. On folate or B12 replacement therapy.	**1:** Direct measurement Blood test with cut off of B12≤ 150 pmol/L being low. 2nd cut off: B12≤ 250 pmol/L being low **Risk factor/exposure 2:** Folate **Method of assessing risk factor/exposure 2:** Direct measurement Blood test with cut off of ≤ 10 nmol/L being low. 2nd cut off: ≤ 12 nmol/L being low. **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Baseline cognitive status **Method(s) of assessing cognitive status:** DSM III R **Informant interview?:** Yes	**2) Important baseline differences:** Patient with low B12 scores were less educated at baseline. Patient with low Folate scores were lower MMSE scores at baseline. **3) Outcome of interest #1** RR risk of incident AD during the three year follow up after adjusting for ages, sex and education: B12 ≤ 150 VS ≥150 pmol/L = 1.6 , 95% CI 0.9, 2.8 Folate ≤ 10 VS ≥10 nmol/L= 1.7 95% CI 1.0, 3.4 Both B12 and Folate: 2.1; 95% CI 1.4, 3.8 **4) Outcome of interest #2** When low levels were defined as B12 ≤250 pmol/L and folate ≤12 nmol/L, the adjusted RR for AD was 7.0 (95% CI 5 1.6 to 31.6) in subjects with MMSE score > 26 and was 1.4 (95% CI 5 0.7 to 2.7) in subjects with MMSE score ≤26 Low levels of vitamin B12 or folate after controlling for age, sex, education and baseline cognitive functioning: 1.4 (0.8–2.4) **5) Outcome of interest #3** No interaction between B12 and folate.	cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Partial. Not sure if either b12 or folate approach is entirely valid.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Wengreen, Munger, Corcoran, et al., 2007 Cache County Study	**Geographical location:** Cache County, UT **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3832 **Duration of follow up:** average 7.2 yrs **Time from risk factor assessment to final cognitive assessment:** average 7.2 yrs	**Age:** Mean (SD): Male 74.2 (6.5) Female 75.0 (6.8) **Sex:** [n (%)] Female: 2066 (53.9%) Male: 1566 (46.1%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 yo, residents of Cache County **Exclusion criteria:** NR	**Risk factor/exposure 1:** Intake of antioxidants (vitamins C & E and carotenes) **Method of assessing risk factor/exposure 1:** Self-report Dietary food frequency questionnaire **Covariates/potential confounders adjusted for in analyses:** Several different models with different adjustments **Method(s) of assessing cognitive status:** Modified MMSE (3MS). Conducted in person at baseline and at f/u visits 2 and 3. **Informant interview?:** No	**1) Follow-up rate:** 3632/3832 (94.8%) **2) Important baseline differences:** Higher baseline 3MS scores in individuals with increasing quartiles of Vitamin C intake alone and combined with Vitamin E **3) Outcome of interest #1** Lower levels of intake of vitamin C, E and carotene had greater acceleration of the rate of 3MS decline over time compared to those with higher levels of intake. Conclusion: "High antioxidant intake from food and supplement sources of vitamin C, vitamin E, and carotene may delay cognitive decline in the elderly." **4) Outcome of interest #2** See Table 3 for differences in mean baseline MS3 score across increasing quartile of intake of vitamins. p-trend reported across quartiles of intake. No single measure of association reported.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Wetherell, Reynolds, Gatz, et al., 2002 Swedish Adoption/T	**Geographical location:** Sweden **Setting:** Community	**Age:** Mean (SD): 63.7 (8.6) **Sex:** [n (%)] Female: 416 (59.0%) Male: 288 (41.0%)	**Risk factor/exposure 1:** Anxiety/neuroticism **Method of assessing risk factor/exposure 1:**	**1) Follow-up rate:** 75.5% **2) Important baseline differences:** NR **3) Outcome of interest #1**	**Comments:** Random effects model for analysis **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
win Study of Aging	**Study design:** Prospective cohort **Number of participants enrolled:** 704 **Duration of follow up:** Up to 9 years **Time from risk factor assessment to final cognitive assessment:** NR	**Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** Same sex twins born between 1886 and 1958 reared apart & control group reared together matched on gender, age, county of birth Age >=50 during study **Exclusion criteria:** Dementia at anypoint in f/u	Self-report – 9-item short-form of the Eyesenck Personality Inventory Neuroticism Scale **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level **Method(s) of assessing cognitive status:** Other – 11 cognitive measures: Wechsler Adult Intelligence Scale Infomration subtest; Synonymes; Analogies; Figure Logic; Koh's Block Design; Card Rotations; Figure Identifiiation; Symbol Digit; Digit Span, Names and Faces Pairs; Thurstone's Picture Memory **Informant interview?:** No	No significant association between neuroticism and cognitive change for any of the measures	2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No, neuroticism is a proxy for anxiety and not a clinical disorder. 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Partial, not given for exposed/unexposed. 10) Analysis controls for confounding? Partial, does not control for other psychiatric conditions. 11) Analytic methods appropriate? Yes
Williamson, Espeland, Kritchevsky, et al., 2009	**Geographical location:** Winston Salem, NC and Palo Alto, CA USA	**Age:** Mean (SD): 77.4 (4.3) **Sex:** [n (%)] Female: 72 (70.6)	**Risk factor/exposure 1:** Physical exercise **Method of assessing**	**1) Follow-up rate:** 93/102 had cognitive testing at final time point **2) Important baseline differences:**	**Comments:** Question 2 **Quality assessment:** *For RCTs:*

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Setting: Community **Study design:** RCT **Test intervention:** Physical activity: combination of aerobic, strength, balance and flexibility over a period of 12 mos **Comparator intervention(s):** Successful aging health education **Number of participants enrolled:** 102 **Duration of follow up:** 1 year **Time from risk factor assessment to final cognitive assessment:** Not applicable	Male: 30 (29.4) **Race/ethnicity:** [n (%)] Caucasian: 83 (81.4) African Am: 14 (13.7) Hispanic: 2 (2.0) Other/mixed: 2 (2.0) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Age 70-89 years. Sedentary life style (< 20 min/wk in structured physical exercise), able to walk 400 m within 15 minutes without sitting and without using any assistive device, Short Physical Performance Battery **Exclusion criteria:** NR	**risk factor/exposure 1:** Self-report Direct measurement **Covariates/potential confounders adjusted for in analyses:** Baseline cognitive status Clinical site **Method(s) of assessing cognitive status:** Other – longitudinal change on cognitive tests (DSST, RAVLT, 3MS, modified Stroop) from baseline to 12 mos **Informant interview?:** No	No differences on a number of demographic, medical, and function variables **3) Outcome of interest #1** Intervention group showed slight improvement on DSST at 12 mos, but difference not significant. Change on the other measures favored the non-intervention group, but differences were not significant. **4) Outcome of interest #2** Outcome that is indirectly related to outcomes of interest: Improvement in DSST was associated with improvement in total Short Physical Performance Battery, chair stand score, and balance score.	1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? No 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed?: Yes 6) Differential dropout rate < 10%? Yes 7) Overall dropout rate < 30%? Yes 8) Conflict of interest reported and insignificant? Can't Tell 9) Randomization adequate? Yes 10) Allocation concealment adequate? Can't Tell
Willis, Tennstedt, Marsiske, et al., 2006 Advanced Cognitive training for Independen	**Geographical location:** Birmingham Al; Detroit Mich; Boston Mass; Baltimore Md; Indianapolis In; State College Pa; **Setting:**	**Age:** Mean (SD): 73.6 **Sex:** [n (%)] Female: 2078 (74.16%) Male: 754 (25.84%) **Race/ethnicity:** [n (%)]	**Risk factor/exposure 1:** Not Applicable – measuring training versus no training **Covariates/potential confounders adjusted for in**	**1) Follow-up rate:** 2832 enrolled 2802 analyzed (ITT) Total attrition at 5 years – 1077 1755/2832= 62% 245 died; 595 withdrew; 214 were excluded by administrative decision and 23 were withdrawn by the family.	**Comments:** Good quality RCT. There may be some differences between the participants of this study and a community population. *For RCTs:* 1) Baseline comparability? Yes 2) Valid AD/cognitive outcomes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
t and Vital Elderly. (ACTIVE)	Other – [specify] Senior Housing Community Centers Hospitals Clinics **Study design:** RCT **Test intervention:** Reasoning Training Memory Training Speed Training. **Comparator intervention(s):** No Training (Control) **Number of participants enrolled:** 2832 **Duration of follow up:** 5 years **Time from risk factor assessment to final cognitive assessment:** 5 years	26% Black **Baseline cognitive status:** MMSE ≥ 23 No self reported AD **Inclusion criteria:** NR **Exclusion criteria:** < 65 yrs of age; functional impairment (≥2ADLdisabilities) cognitive decline (MMSE score ≤22); self reported AD; medical conditions associated with imminent functional decline or death; severe losses in vision, hearing, or communicative ability that would interfere with study participation; recent cognitive training; unavailable during the study period	**analyses:** Age Baseline cognitive status for those who did booster training since they were younger and had higher mmse scores For non booster analysis independent variables were: 'Fixed effects for treatment group, time, assignment to booster training, field site. time x training, booster x training' **Method(s) of assessing cognitive status:** MMSE Other – Self Reported AD **Informant interview?:** No	**2) Important baseline differences:** participants who were randomized to booster training were younger (*P*=.007) and had higher baseline MMSE scores (*P*=.008) compared with participants who were eligible and not assigned to booster training **3) Outcome of interest #1** Effect of Training on Cognitive Outcomes From Baseline to Year 5 presented as Mean change from baseline to year 5; Effect size (99% CI) Memory Training (outcome Memory) = −1.0 ; 0.23 (0.11 to 0.35**)** Reasoning Training (outcome reasoning)= 8.1 ; 0.26 (0.17 to 0.35) Speed Training (outcome processing speed) = 241.8; 0.76 (0.62 to 0.90) Speed Training (outcome reasoning) = 119.6; 0.15 (0.01 to 0.29) **4) Outcome of interest #2** Effect of Booster Training on Cognitive Outcomes From Baseline to Year 5 after controlling for baseline age and MMSE score presented as Effect size (99% CI) Reasoning Training (outcome reasoning)= 0.28 (0.12 to 0.43) Speed Training (outcome processing speed) = 0.85 (0.61 to 1.09) **5) Outcome of interest #3** None of the effect sizes for effect of training on functional outcomes from baseline to Year 5 reached statistical	assessment? Partial. The speed of processing task was invented by an ACTIVE investigator (or at least she owns part of the company). It is not clear that it is a validated test for this purpose. 3) Subjects/providers blind? Partial 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed? Yes 6) Differential dropout rate < 10%? No 7) Overall dropout rate < 30%? No 8) Conflict of interest reported and insignificant? Partial 9) Randomization adequate? Yes 10) Allocation concealment adequate? Can't Tell

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				significance at the 99% confidence interval.	
Wilson, Bennet, Bienias, et al., 2003 Chicago Health Aging Project.	**Geographical location:** Chicago, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 6158 enrolled. 1175 dies before first follow up. Of 4983 alive, 4392 completed first follow up (88.1%). This was considered to be the study sample. **Duration of follow up:** 5.3 years **Time from risk factor assessment to final cognitive assessment:** 6 years. Interviews done over 3 yr intervals. Average of 2.6 interviews per person.	**Age:** Mean (SD): 73.9 (6.5) **Sex:** [n (%)] Female: 2727 (62%) Male: 1665 (38%) **Race/ethnicity:** [n (%)] AA: 2710 (61.7%) Other: 1682 (38.3%) **Baseline cognitive status:** All (none excluded based on cognitive status) **Inclusion criteria:** Residents of the Chicago area. ≥ 65 yrs of age. **Exclusion criteria:** NR	**Risk factor/exposure 1:** Cognitive activity. **Method of assessing risk factor/exposure 1:** Self-report of number of activities on a 5 point scale- then converted into a composite score. **Risk factor/exposure 2:** Depression **Method of assessing risk factor/exposure 2:** Self-report CESD **Covariates/potential confounders adjusted for in analyses:** [delete any from the list below that do not apply and add items as needed] Age Race Sex Educational level **Method(s) of assessing cognitive status:**	**1) Follow-up rate:** Can't tell. It appears that 88.1% of those alive at the first follow up completed at least one follow up interview and were included in the analysis. However, the number of participants who completed the second follow up is unknown. **2) Important baseline differences:** Can't tell. **3) Outcome of interest #1** The rate of cognitive decline was 0.064 units per year on the global measure of cognition Frequency of cognitive activity was associated with rate of cognitive decline. For each point on the cognitive activity scale, cognition decreased by 0.012 units, or about 19%. SE= 0.003, P <0.001 Compared to a person with infrequent cognitive activity (score = 2.14,10th percentile), rate of global cognitive decline was reduced by about 35% in a person with frequent cognitive activity (score = 4.00, 90th percentile) **4) Outcome of interest #2** After controlling for disability, number of medical conditions, CES-D score,	**Comments:** Since participants of all cognitive levels were included, this could introduce some differences in prognosis within the sample. . **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Partial, 79% of the community responded to the invitation to participate. But all cognitive levels included. 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Partial. Not controlled for baseline cognitive function. 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Other – [specify] Cognitive change on global index of cognitive function. **Informant interview?:** No	age, sex, race, and education, cognitive activity continued to be related to reduced cognitive decline (estimate = 0.010, SE = 0.004, p =0.003).	
Wilson, Bienias, Berry-Kravis, et al., 2002 Religious Orders Study	**Geographical location:** 40 sites across the USA **Setting:** Community - Religious orders **Study design:** Prospective cohort **Number of participants enrolled:** 669 **Duration of follow up:** 2-8 years Annual assessment Average 5.9 to 6 **Time from risk factor assessment to final cognitive assessment:** Up to 8 years	**Age:** Means(sd) e2: 75.7 (7.3) yrs e3: 75.7 (6.7) yrs e4 74.8 (6.3) yrs **Sex:** [n (%)] Female: 435 (65%) Male: 234 (35%) **Race/ethnicity:** [n (%)] 622 (93%) white non-hispanic **Baseline cognitive status** Non-demented **Inclusion criteria:** Religious orders member at 1 of 40 groups. Age at least 65. Not demented **Exclusion criteria:** Dementia.	**Risk factor/exposure 1:** Apolipoprotein E ε4 APOE ε4 **Method of assessing risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Time since baseline **Method(s) of assessing cognitive status:** 19 tests 7 assessed episodic memory (world list memory, recall, and recognition; immediate and delayed recall logical memory and East Boston); Semantic memory (verbal fluency);	**1) Follow-up rate:** 98% **2) Important baseline differences:** NR **3) Outcome of interest #1** **Random effects model** Rate of episodic memory change ε2/2 or 2/3: +.016 ε3/3: -.022 ε4/4 or 3/4: -.073 ε2 vs ε3/3 p<.05 ε4 vs ε3 p<.001 No difference between ε2 and ε3 in other cognitive domains ε4 declined more rapidly than ε3/3 in semantic memory and perceptual speed, but not in working memory or visuospatial ability ε2 semantic memory decline is slower than ε3/3, but there is no effect in other cognitive domains.	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? 2) Partial. Required participants agree to autopsy. 3) Selection minimizes baseline differences in prognostic factors? Yes 4) Sample size calculated/5% difference? No 5) Adequate description of the cohort? Yes 6) Validated method for ascertaining exposure? Yes 7) Validated method for ascertaining clinical outcomes? Partial 8) Outcome assessment blind to exposure? Yes 9) Adequate follow-up period? Yes 10) Completeness of follow-up? Yes 11) Analysis controls for confounding? Yes 12) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Boston naming; National adult reading test; extended range vocabulary; Working memory (digits forward, digits backward, digit ordering and alpha span); Perceptual speed (symbol digit modalities test and number comparison); visuospatial ability (judgment of line orientation, standard progressive matrices). Other – rate change cognitive test **Informant interview?:** No		
Wilson, Hebert, Scherr, et al., 2009 Chicago Health and Aging Project	**Geographical location:** Southside Chicago USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 6533 **Duration of follow up:** 6.5 (SD = 3.6) **years**	**Age:** Mean (SD): 72.2 years (SD = 6.1) **Sex:** [n (%)] Female: 61% Male: 39% **Race/ethnicity:** [n (%)] 67% were African American **Baseline cognitive status:** All **Inclusion criteria:** Older residents of the	**Risk factor/exposure 1:** Educational attainment **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Five chronic medical conditions was	**1) Follow-up rate:** 10,068 people interviewed at baseline 1,552 died before the first follow-up interview and 1,580 had not yet reached the date scheduled for the first follow-up. Among the 6,936 eligible for follow-up, 6,533 (94%) completed at least one follow-up interview. **2) Important baseline differences:** Higher education associated with younger age ($p < 0.001$) and white race ($p < 0.001$) **3) Outcome of interest #1** No linear association between	**Comments:** Question 2 – no cat Dx **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes?

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		Chicago Southside area.	obtained from self report of heart attack or myocardial infarction, hypertension, stroke, diabetes mellitus, and cancer **Method(s) of assessing cognitive status:** Other – longitudinal change on the immediate and delayed recall of the East Boston Story Oral form of the Symbol Digit Modalities Test Mini-Mental State Examination **Informant interview?:** No	education and rate of change in cognitive function. Models that allowed for non-linearity in education and its relation to cognitive decline showed that education was associated with change in cognitive performance over time (coefficient >-0.001; se: <0.001; p = 0.005). The rate of cognitive decline at average or high levels of education was slightly increased during earlier years of follow-up but slightly decreased in later years in comparison to low levels of education. Findings were similar among black and white participants. **4) Outcome of interest #2** Cognitive performance improved with repeated test administration, but there was no evidence that retest effects were related to education or attenuated education's association with cognitive change (Education x retest 4: coefficient <-0.001; se: 0.039; p = 0.990)	Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
	Time from risk factor assessment to final cognitive assessment: 6.5 (SD = 3.6) years	Completed at least one follow up interview. **Exclusion criteria:** NR			
Wilson, Krueger, Arnold, et al., 2007 Rush Memory & Aging Project	**Geographical location:** Chicago, IL **Setting:** Community **Study design:** Prospective cohort	**Age:** Mean (SD): 80.7 (7.1) **Sex:** [n (%)] Female: 600 (75.8%) Male: 192 (24.2%) **Race/ethnicity:** [n (%)]	**Risk factor/exposure 1:** Loneliness **Method of assessing risk factor/exposure 1:** Self-report – de Jong Gierveld Loneiness Scale (range 0-	**1) Follow-up rate:** 92.3% **2) Important baseline differences:** NR **3) Outcome of interest #1** After adjusting for age, sex, and level of educational achievement, risk of clinical AD (76 subjects) increased	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Partial 2) Selection minimizes baseline differences in prognostic factors? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Number of participants enrolled: 857; 791 analyzed **Duration of follow up:** Mean 3.3 years. Range: 2-5 years. **Time from risk factor assessment to final cognitive assessment:** Mean 3.3 years. Range: 2-5 years.	African-American 46 ((5.8%) Other 746 (94.2%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participant in Rush Memory and Aging Project; agreement to annual in-home clinical evaluations; agreement of brain donation upon death; completed at least one follow-up evaluation **Exclusion criteria:** Dementia Dx @ baseline	5)(Questionnaire) **Risk factor/exposure 2:** Social isolation (social network size [#] and participation in social activity (0-5 scale) **Method of assessing risk factor/exposure 2:** Self-report **Covariates/potential confounders adjusted for in analyses:** age, sex, and level of educational achievement and for social activity, social network, physical activity, cognitive activity, depressive symptoms, income, race/ethnicity, disability, and vascular risk factors **Method(s) of assessing cognitive status:** NINCDS-ADRDA **Informant interview?:** NO	by approximately 51% for each point on the loneliness scale (relative risk [RR], 1.51; 95% [CI], 1.06-2.14) Social activity (0-5): RR 0.52 (95% CI 0.34 to 0.79) Social network size: RR 1.01 (95% CI 0.97 to 1.05) **4) Outcome of interest #2** Relation of loneliness to AD incidence after controlling for social network and social activity in the above model: RR, 1.45; 95% CI, 1.01-2.09 Additional analyses showed the association between loneliness and AD was unchanged after controlling for income, disability on the Katz scale and vascular risk factors and conditions. **5) Outcome of interest #3** Relation of Loneliness to Change in Cognitive Function after controlling for age, sex, and level of educational achievement in separate mixed effect models: Global cognition: Loneliness x time Estimated SE: -0.01 (0.01) P = .03 Episodic memory: Loneliness x time Estimate (SE) 0.00 (0.01) p = .79 Semantic memory: Loneliness x time Estimate (SE) −0.02 (0.01) p = .01 Working memory: Loneliness x time Estimate (SE) −0.02 (0.01) p = .09	3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				Perceptual speed: Loneliness x time Estimate (SE) −0.02 (0.01) p = .03 Visuospatial ability: Loneliness x time Estimate (SE) −0.03 (0.01) p = .04	
Wilson, Mendes De Leon, Barnes, et al., 2002 RELIGIOUS ORDERS STUDY	**Geographical location:** U.S. **Setting:** Community –Religious Orders **Study design:** Prospective cohort **Number of participants enrolled:** 879 screened; 801 eligible **Duration of follow up:** Mean 4.5 years **Time from risk factor assessment to final cognitive assessment:** Mean 4.5 years	**Age:** Range: Incident AD: 81.1(6.2) No AD: 74.3 (6.3) **Sex:** Incident AD (n=111) Female: 74 (66.7%) Male: 37 (33.3%) No AD (n=622) Female: 418 (67.2%) Male: 204 (32.8%) **Race/ethnicity:** Incident AD White, non-Hispanic = 105 (94.6%) No AD White, non-Hispanic =562 (90.4%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 years at baseline Consent to annual clinical evaluations Consent to brain	**Risk factor/exposure 1:** Cognitive activity frequency. **Method of assessing risk factor/exposure 1:** Self-report 7 common activities that involve information processing. Frequency rated on a 5-point scale: 5) 5 points: every day or about every day. 4) 4 points: several times a week. 3) 3 points: several times a month. 2) 2 points: several times a year. 1) once a year or less. **Covariates/potential confounders adjusted for in analyses:** Age Gender Education Cognitive activity score	**1) Follow-up rate:** 724/801 (90%) **2) Important baseline differences:** NA **3) Outcome of interest #1** Annual Rate of Change in Specific Cognitive Functions: Association with Cognitive Activity Frequency Estimate (SE), p value Working memory: 0.021 (0.008), p=.007 Perceptual speed: 0.026 (0.012), p=0.02 In random-effects models, a 1-point increase in cognitive activity was associated with reduced decline in global cognition (by 47%), working memory (by 60%), and perceptual speed (by 30%). **4) Outcome of interest #2** RR of Incident AD by Cognitive Activity Frequency Score: RR 0.67 (95% CI: 0.49, 0.92) A 1-point increase in cognitive activity score was associated with a 33% RR of AD (hazard ration, 0.67;	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial. Required agreeing to autopsy as part of enrollment. 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Can't Tell 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		donation at the time of death **Exclusion criteria:** Dementia at baseline	**Method(s) of assessing cognitive status:** 20 cognitive tests administered in a 45-minute session. MMSE for descriptive purposes. 7 tests of episodic memory; 4 tests of working memory; 2 tests of perceptual speed; and 2 tests of visuospatial ability Composite measures of global cognition. AD diagnosed according to NINCDS/ADRDA **Informant interview?:** No	95% CI: 0.48, 0.92) **5) Outcome of interest #3** Results were comparable when terms for ApoE were added to the model. **6) Outcome of interest #4** Physical activity was not associated with risk of AD (HR, 1.00; 95% CI, 0.97-1.02).	
Wilson, Scherr, Hoganson, et al., 2005 Religious Order Study	**Geographical location:** Multiple US sites **Setting:** Community - members of Religious Orders **Study design:** Prospective cohort **Number of participants enrolled:** 859 **Duration of follow up:**	**Age:** Mean (SD): 75.0 (7.0) **Sex:** Female: 596 (69.4%) Male: 263 (30.6%) **Race/ethnicity:** African-American: 71 (8.3%) Other: 787 (91.7%) **Baseline cognitive status:** Non-demented	**Risk factor/exposure 1:** Early life socioeconomic status (SES) indicators **Method of assessing risk factor/exposure 1:** Self-report SES: 1) parental education, 2) paternal occupation, 3) # of children in the family.	**1) Follow-up rate:** 859/ 877 – 98% **2) Important baseline differences:** NA **3) Outcome of interest #1** 154 incident cases of AD. **4) Outcome of interest #2** Neither early life household (RR: 1.12, 95% CI: 0.88,1.42) nor community SES (RR: 1.35, 95% CI: 0.93, 1.96) was related to risk of AD. (RR is for a 1-unit increase in each	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Mean: 5.6 years **Time from risk factor assessment to final cognitive assessment:** Mean: 5.6 years	**Inclusion criteria:** Catholic nuns, priests, and brothers from the Religious Orders Study **Exclusion criteria:** Dementia at baseline	Also, 3 other SES indicators based on county of birth: 4) literacy rate, 5) % of children in county in school, 6) Duncan SES. The 7th SES indicator was participant's own education level attained. Summary measures used for early life household and community SES level. **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level SES indicators **Method(s) of assessing cognitive status:** NINCDS-ADRDA Other: change in performance on cognitive tests over time **Informant interview?:** No	SES indicator) No significantly different findings when quadratic terms for SES indicators added. 5) Outcome of interest #3 Higher SES was related to slightly greater decline on semantic memory task. There were no other significant associations between independent variables and cognitive change over time.	6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Wilson,	**Geographical**	**Age:**	**Risk factor/exposure**	**1) Follow-up rate:**	**Comments:**

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Scherr, Schneider, et al., 2007 RUSH MEMORY AND AGING PROJECT	**location:** Chicago area, USA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 931 with baseline evaluation; 829 eligible at one year follow-up **Duration of follow up:** Mean of 3.5 (sd = 1.2) annual follow up assessments. Range: 2 – 6 follow-ups **Time from risk factor assessment to final cognitive assessment:** Mean of 3.5 (sd = 1.2) annual follow up assessments. Range: 2 – 6 follow-ups	Mean (SD): 80.4 (7.4) **Sex:** Female: 581 (75%) Male: 194 (25%) **Race/ethnicity:** White (non-Hispanic): 705 (91%) Other: 70 (9%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participating in the Rush Memory and Aging Project Agree to annual clinical evaluation Agree to donate brain at death **Exclusion criteria:** Dementia at baseline	**1:** Cognitive activity participation **Method of assessing risk factor/exposure 1:** Self-report. Structured questionnaire at baseline. Frequency of participate on a 5-point scale, from 1 = once a year or less, to 5= every day or about every day. **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level **Method(s) of assessing cognitive status:** NINCDS-ADRDA MCI classified as evidence of impairment in at least one cognitive domain in the absence of dementia. Other: change in performance on cognitive tests over	775/829 (93.5%) with f/u data **2) Important baseline differences:** NR by cognitive activity level **3) Outcome of interest #1** More frequent current cognitive activity was associated with reduced incidence of AD (RR _ 0.58; 95% CI: 0.44, 0.77). More frequent past cognitive activity was also associated with reduced risk of AD (RR _ 0.56; 95% CI: 0.36, 0.88) **4) Outcome of interest #2** more frequent cognitive activity was associated with reduced incidence of MCI (RR _ 0.71; 95% CI: 0.58, 0.87). 5) Outcome of interest #3 More frequent current cognitive activity associated with less decline on global cognitive measure Estimate = 0.025; se=0.010; p = 0.015	None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No 6) Validated method for ascertaining clinical outcomes? Partial 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			time **Informant interview?:** No		
Wilson, Schneider, Boyle, et al., 2007 Religious Orders Study & Rush Memory and Aging Project	**Geographical location:** Chicago, USA & other USA locations **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1256 **Duration of follow up:** RMAP = 3.9 and for the combined group = 6.2 mean annual evaluations Range 1 – 13 yrs **Time from risk factor assessment to final cognitive assessment:** RMAP = 3.9 and for the combined group = 6.2 mean annual evaluations Range 1 – 13 yrs	**Age:** Mean (SD): 76.8(7.7) **Sex:** [n (%)] Female: 888(70.7%) Male: 368 (29.3%) **Race/ethnicity:** [n (%)] 1143 (91%) White non-Hispanic **Baseline cognitive status:** Non-demented **Inclusion criteria:** Catholic nuns priests and brothers who agreed to brain donation at death (ROS study) or participant in RMAP At least 1 year f/u Valid score on NEO neuroticism scale **Exclusion criteria:** Dementia or MCI	**Risk factor/exposure 1:** Depression – 10-item CESD 2: Distress proneness – 6 items from the 12-item NEO Five Factor Inventory (score ranges 0- 48) **Method of assessing risk factor/exposure 1:** Self-report at baseline **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level **Method(s) of assessing cognitive status:** NINCDS-ADRDA for AD MCI – cognitive impairment w/o meeting criteria for dementia **Informant interview?:** No	**1) Follow-up rate:** 95.2% **2) Important baseline differences:** Can't tell **3) Outcome of interest #1** Association with MCI CESD for each depressive symptom, RR=1.06 (95% CI 1.002 to 1.120) Distress proneness RR for each one point increase = 1.02 (95% CI 1.01 to 1.04) When controlling for CESD score the association between distress proneness and MCI was not substantially changed, RR 1.02, 1.01 to 1.04 When controlling for distress proneness score the association between CESD and MCI was not significant RR=1.02, 0.96 to 1.09	**Comments:** Unclear CESD-10 scoring; unclear if association is for each one point increase or each symptom endorsed **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Partial. Required agreeing to autopsy. 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No 4) Adequate description of the cohort: Yes 5) Validated method for ascertaining exposure: Partial 6) Validated method for ascertaining clinical outcomes: Partial 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Yes 9) Completeness of follow-up: Yes 10) Analysis controls for confounding: Yes 11) Analytic methods appropriate: Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Winnock, Letenneur, Jacqmin-Gadda, et al., 2002 PAQUID	**Geographical location:** Gironde, France **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2792 in PAQUID. Of these, 626 initially eligible by volunteering for APOE testing. **Duration of follow up:** Mean NR. Range: 1-8 yrs. **Time from risk factor assessment to final cognitive assessment:** Mean NR. Range: 1-8 yrs.	**Age at baseline:** Mean (SEM): 73.7 (0.26) Range: 65-94 **Sex:** NR **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 yrs, living in southern France. Participants of PAQUID study who volunteered to give a blood sample for APOE phenotyping at the 1sr year f/u interview. **Exclusion criteria:** Dementia at baseline and at 1st year of f/u.	**Risk factor/exposure 1:** Education **Method of assessing risk factor/exposure 1:** Self-report **Risk factor/exposure 2:** APOE **Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Sex Education Time Age by time APOE Random effects linear regression model, which takes into account the lack of independence of a subject's measurements across time. **Method(s) of**	**1) Follow-up rate:** 2792 in PAQUID. 626 in this study because they volunteered for APOE testing. Two analyses: 1) Excluded dementia at baseline or 1st yr f/u (n=26). Sample size: 600/626 = 96% 2) Excluded dementia at baseline, 1st year or 3rd year f/u (n=53). Sample size: 547/626 = 87% MMSE f/u rates: 1-yr: 574 (95.7%) 3-yr: 508 (84.7%) 5-yr: 457 (76.2%) 8-yr: 364 (60.7%) Four MMSE measurements available in 332 participants (55.3%) **2) Important baseline differences:** NA **3) Outcome of interest #1--APOE** APOE was significantly associated with lower cognitive performance at baseline. Course of cognitive performance during the f/u was the same for both APOE carriers and noncarriers. **4) Outcome of interest #2—APOE and education** Lower education level was associated with lower cognitive performance at baseline, and the	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			assessing cognitive status: Assessments at 1, 3, 5, 8, & 10 yrs after baseline visit. Cognitive performance evaluated at each visit with a comprehensive battery of tests. DSM-IIIR for dementia, followed by neurologist evaluation to confirm diagnosis of dementia. Main outcome: MMSE scores at multiple timepoints **Informant interview?:** No	effect of an APOE allele on cognitive performance disappeared after adjustment for education. APOE carriers show decreased MMSE scores compared with non-carriers, but the effect of APOE on cognition disappears after adjustment for education. Non-demented elderly people maintain a stable cognitive performance regardless of the their APOE phenotype. **5) Outcome of interest #3** Conclusions: 1) Baseline cognition related to APOE phenotype 2) APOE effects disappeared after adjustment for education 3) No global cognitive decline observed over time among non-demented participants 4) Level of global cognitive performance remained stable throughout f/u and was independent of APOE phenotype.	
Wright, Elkind, Luo, et al., 2006 Northern Manhattan Study	**Geographical location:** Northern Manhattan, NY, USA **Setting:** Community	**Age:** Mean (SD): 71 yr (9) **Sex:** Female: 957 (67%) Male: 471 (33%) **Race/ethnicity:** [n (%)]	**Risk factor/exposure 1:** Alcohol **Method of assessing risk factor/exposure 1:** Self-report- at cognitive	**1) Follow-up rate:** NR (cannot tell how many of those not included in analyses actually dropped out vs were missing alcohol data) **2) Important baseline differences:** Trend ($p<0.0001$) toward those	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
(NOMAS)	**Study design:** Prospective cohort **Number of participants enrolled:** 1428 analytical sample **Duration of follow up:** Mean 2.2 yrs (range 0.5-4.4) **Time from risk factor assessment to final cognitive assessment:** Mean 2.2 yrs (range 0.5-4.4)	NR **Baseline cognitive status:** NR **Inclusion criteria:** At least 40 yrs old, no history of stroke, resident of North Manhattan for at least 3 mos, have a phone **Exclusion criteria:** None except as covered by inclusion criteria.	baseline asked questions about alcohol intake during past six months; details of quantity of wine, beer, and liquor were collected **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Baseline cognitive status Interval between cognitive testing Health insurance status HDL-C level BMI History of hypertension Diabetes Cardiac disease Smoking Depression Physical activity **Method(s) of assessing cognitive status:** Other – longitudinal performance on the TICS-m **Informant interview?:** No	drinking less or no alcohol being younger, more likely to be female, had less than 8 yrs education, less likely to have insurance, more likely to be Hispanic, more likely to have hypertension, more likely to have diabetes, more likely to smoke, more likely to have a higher BMI, more likely to be depressed, and more likely to be physically active. Individuals who drank 1 drink/month to <1/week or > 2/day had higher homocysteine levels than never drinkers. Individuals who drank 1/week or more had higher baseline TICS-m scores than nondrinkers. **3) Outcome of interest #1** Drinking less than one drink a week (P=0.09), between one drink weekly up to two drinks daily (P=0.001), and more than two drinks daily (P=0.003) were associated with less cognitive decline on the modified Telephone Interview for Cognitive Status (TICS-m) compared to never drinkers.. **4) Outcome of interest #2** This dose-response relationship was not modified by the presence of an APOE-4 allele in a subsample	differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Partial 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Xu, von Strauss, Qiu, et al., 2009 Kungsholmen	**Geographical location:** Kungsholmen district of Stockholm, Sweden. **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1248 **Duration of follow up:** 9 year; **(**mean per person=5.1 years; maximum=10.5 years) **Time from risk factor assessment to final cognitive assessment:** ~6 yr	**Age:** Mean (SD): nl 81.4 (4.9) borderline DM 82.2 (5.2) DM 81.6 (5.2) **Sex:** [n (%)] Female: 74.7% Male: 25.3% **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** all registered inhabitants who were living in the Kungsholmen district of Stockholm, Sweden, and were aged ≥75 years on 1 October 1987 were initially invited to participate in the project. **Exclusion criteria:** dementia	**Risk factor/exposure 1:** Diabetes mellitus **Method of assessing risk factor/exposure 1:** Direct measurement Medical record Other – medication use **Covariates/potential confounders adjusted for in analyses**: Age, sex, education, baseline MMSE score, BMI, APOE genotype and vascular disorders (i.e. heart disease, stroke, antihypertensive drug use and BP) were considered as potential confounders**.** **Method(s) of assessing cognitive status:** DSMIII-R **Informant interview?:** No	**1) Follow-up rate:** 1248/1475 = 84.6 **2) Important baseline differences:** MMSE score; presence of heart disease; diastolic BP; use of antihypertensive drugs differ in nondiabetic, borderline and DM groups **3) Outcome of interest #1** Fully adjusted model AD with stroke Non-diabetic HR 1 Borderline DM 1.93 (.59-6.28) Undiagnosed DM 3.75 (.48-4.55) AD without vasc comorbidities Non-diabetic 1 Borderline HR 2.85 (1.29-6.3) Undiagnosed DM 4.74 (1.08-18.46) **4) Outcome of interest #2** Normal 1 Borderline HR 1.87 (1.11-3.14) <7.8mmol OR 0.34 (0.05-2.43) 7.7-11mmol 1.26 (0.46-3.62) >11mmol 1.08 (0.4-2.95) Undiagnosed DM 3.29 (1.2-9.01)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Yaffe, Barnes,	**Geographical location:**	**Age:** Mean (SD): 70.8 ±4.7	**Risk factor/exposure 1:**	**1) Follow-up rate:** There were 7701 women who had a	**Comments:** Question 2, no dx

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Nevitt, et al., 2001 Study of Osteoporotic Fxs	Baltimore, Minneapolis, Monongahela Valley (near Pittsburgh), Portland Oregon **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 5925 **Duration of follow up:** Mean 7.5 yrs range **Time from risk factor assessment to final cognitive assessment:** Mean 7.5 years. Follow-up at both 6 and 8 years after initial assessment	Range: ≥65 **Sex:** [n (%)] Female: 100% **Race/ethnicity:** [n (%)] Black women excluded **Baseline cognitive status:** shortened mmse ≥ 23/26 **Inclusion criteria:** Participant in the Study of Osteoporotic Fractures. **Exclusion criteria:** Shortened mmse < 23/26, women unable to stand up unaided from chair or walk up stairs (self reported), black women, women with missing baseline cognitive score, women with baseline physical limitations, women with missing information on physical limitations, women who did not complete baseline physical activity assessments	Physical activity **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age, Educational level Health status, functional limitation, depression score, stroke, dm, htn, mi, smoking, estrogen use **Method(s) of assessing cognitive status:** change in shortened mmse score. Change of ≥ 3 points over period of follow up defined cognitive decline. **Informant interview?:** No	high enough baseline cognitive score and who did not report physical limitations at baseline. Of these, 8% (596) died, 3% were lost (238), 12% (942) did not have follow up cognitive testing, leaving 5925/7701 or 77% **2) Important baseline differences:** Physical activity divided into quartiles. Those in higher quartiles were younger, more educated, more likely to drink and take estrogen, less likely to smoke with a lower bmi, lower depression scores, fewer medical comorbidities and less functional limitation. **3) Outcome of interest #1** Using lowest quartile of blocks walked per week as reference: Second had OR 0.87 (0.72 – 1.05) third OR 0.63 (0.52-0.77) highest quartile had OR 0.66 (0.54 – 0.82) Using total kilocalories per week into quartiles with the lowest as the reference: again OR Second 0.90 (0.74-1.09) Third 0.78 (0.64-0.96) Highest 0.74 (0.60-0.90) **4) Outcome of interest #2** Results are presented comparing the second, third and highest quartiles to the lowest with results stratified by age (at 70), by presence or absence of medical comorbidities and by education (at 12 yrs). These results do not appear otherwise adjusted.	I suspect this is a secondary analysis in this study. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort?: Yes 2) Selection minimizes baseline differences in prognostic factors?: Yes 3) Sample size calculated/5% difference?: No 4) Adequate description of the cohort?: Partial 5) Validated method for ascertaining exposure?: Yes 6) Validated method for ascertaining clinical outcomes?: Yes 7) Outcome assessment blind to exposure?: Can't Tell 8) Adequate follow-up period?: Yes 9) Completeness of follow-up?: Yes 10) Analysis controls for confounding?: Yes 11) Analytic methods appropriate?: Yes.

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
				5) Outcome of interest #3 The percentage decline in the shortened mmse score was also treated as a continuous variable. The difference between women in the higher quartiles and those in the lower quartiles was significant (p<0.001) 6) **Outcome of interest #4** cognitive decline (defined as a three or more point drop in screener score) was present in 17% of those in highest activity quartile, 18% next, 22% next and 24% of those in lowest quartile. It is noted that these women had important baseline differences as above, however (particularly age, vascular disease, smoking). Baseline cognitive scores were also reported difference with p=0.001 but difference was between 25.1 in lowed group and 25.2 in other quartiles .	
Yaffe, Blackwell, Gore, et al., 1999 Study of Osteoporotic Fractures	**Geographical location:** Baltimore, MD; Minneapolis, Minn; Monongahela Valley, PA; Portland, OR **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:**	**Age:** Mean (SD): 72.8 (4.7) to 74.0 (5.2) **Sex:** [n (%)] Female: 7511 (100%) Male: 0 (0%) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented	**Risk factor/exposure 1:** Depressive symptoms **Method of assessing risk factor/exposure 1:** Self-report at baseline using the Geriatric Depression Scale (GDS, range 0-15) **Covariates/potential confounders adjusted for in**	**1) Follow-up rate:** 645 died; 5781/7511 had follow-up (76.9%) Women w/o f/u had lower baseline cognitive and depression scores **2) Important baseline differences:** Women with more depressive symptoms were older, reported more functional impairment, were less educated, exercised less, were less likely to report good health status and less likely to be married **3) Outcome of interest #1**	**Comments:** Logistic regression for >=3 point decline in MMSE Only women; blacks excluded **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort: Yes 2) Selection minimizes baseline differences in prognostic factors: Yes 3) Sample size calculated/5% difference: No

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	7511 **Duration of follow up:** 4 years **Time from risk factor assessment to final cognitive assessment:** 4 years	**Inclusion criteria:** Age >=65 yo Community dwelling **Exclusion criteria:** Black race Prior clinical diagnosis of dementia	**analyses:** Age Educational level Baseline cognition Health status Exercise Alcohol use Funcational status Clinic site **Method(s) of assessing cognitive status:** Modified MMSE decline by >=3 points (mMMSE range 0-26) Change in Trails B, Digit symbol and mMMSE **Informant interview?:** No	Incident AD >=3 point decline on mMMSE (n=653 cases): OR for >=6 on GDS=2.1 (1.4-3.1); OR for 3-5 on GDS=1.6 (1.2-2.1) compared to 0-2 on GDS **4) Outcome of interest #2** MMSE decline of >=3 points Subgroup analysis educational level showed: <=8 years: OR for MMSE decline = 0.84 (0.49 to 1.43) > 8 years: 1.83 (95% CI 0.93 to 3.6) **5) Outcome of interest #3** Change in cognition Women with more depressive symptoms had a greater decline in cognitive scores for the Trails B (F=3.64, p=0.03), Digit Symbol (F=3.41, p=0.03) and modified MMSE (F=8.44, p<0.001) A sensitivity analysis excluding women with a modified MMSE of < 20 at baseline or who reported a history of physician-diagnosed stroke, dementia, or Parkinson disease at the time of f/u "did not substantially affect the results." - data not given	4) Adequate description of the cohort: Yes 5) Validated method for ascertaining exposure: Partial; validated scale but symptoms only 6) Validated method for ascertaining clinical outcomes: Partial; uncertain clinical significance 7) Outcome assessment blind to exposure: Can't Tell 8) Adequate follow-up period: Yes 9) Completeness of follow-up: Partial, Loss to f/u associated with cognition and depression 10) Analysis controls for confounding: Yes 11) Analytic methods appropriate: Yes
Yaffe, Cauley, Sands, et al., 1997	**Geographical location:** Monongahela Valley near Pittsburgh, PA	**Age:** Mean (SD): 71 **Sex:** [n (%)] Female: 100%	**Risk factor/exposure 1:** APOE genotype **Method of assessing**	**1) Follow-up rate:** 1248/1750= 71.3% Follow-up cognitive testing in 1138 1138/1248 = 91.2%	**Comments:** None **Quality assessment:** *For observational studies:*

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	Setting: Clinical – Monongahela Valley Clinic of the multicenter Study of Osteoporotic Fractures **Study design:** Prospective cohort **Number of participants enrolled:** 1750 1248 with cognitive testing **Duration of follow up:** Average 6.4 years **Time from risk factor assessment to final cognitive assessment:** 6 years	Male: 0% **Race/ethnicity:** [n (%)] 100% white except for 3 Asian and 1 other. **Baseline cognitive status:** Non-demented **Inclusion criteria:** Women were over the age of 65 and living in the community. They were recruited from 1985 voter registration lists in selected zip codes within approximately 40 km of the clinic. **Exclusion criteria:** Men and black women because of lower risk of osteoporotic fractures. Dementia, Parkinson's disease or stroke.	**risk factor/exposure 1:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Educational level Baseline cognitive status Depression Presence of severe tremor **Method(s) of assessing cognitive status:** Other – Modified MMSE (max score 26 Trails B Digit Symbol Cognitive decline was defined on each or any test if a woman had the largest 10th percentile reduction in performance from initial score to repeat testing. **Informant interview?:** No	**2) Important baseline differences:** none **3) Outcome of interest #1** Presence of an APOE4 was significantly associated with worsening on all cognitive tests at follow-up compared to no E4 group (modified MMSE P=.01; Digit Symbol P=.05; Trails B P=.003) **4) Outcome of interest #2** Incidence of cognitive decline was 1.6 times higher in the E4 group (P<.03) and ranged from 1.2 times higher for Trails B to 2.4 times higher for modified MMSE. Homozygotes declined almost twice as fast as heterozygotes on all tests except Trails B. **5) Outcome of interest #3** Reduction on the modified MMSE was 0% for no E4; 1.9% for 1 E4; and 3.7% for 2 E4s (P<.001) Reduction on Digit Symbol was 6.2% for no E4; 9% for 1 E4 and 17.5% for 2 E4s. (P=.04) Reduction on Trails B was 5.9% for no E4; 25% for 1 E4 and 10.9% on 2 E4s (P=.002)	1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Yaffe, Fiocco, Lindquist, et al., 2009	**Geographical location:** Memphis, TN Pittsburgh, PA	**Age:** Mean (SD): Maintainers 73 (2.6) Minor decline 73.6	**Risk factor/exposure 1:** diabetes	**1) Follow-up rate:** 2509/3075 **2) Important baseline differences:**	**Comments:** Over 8 years, 30% of the participants maintained cognitive function, 53% showed minor decline, and 16% had

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		(2.9) Major decline 74.3 (2.6) Range: 70-79 @ baseline **Sex:** [n (%)] Female: 1334 (53.2%) Male: 1175 (46.8%) **Race/ethnicity:** [n (%)] White 1612 (64.3%) Black 897 (35.7%) **Baseline cognitive status:** 3MS>80 **Inclusion criteria:** a random sample of white and all black Medicare-eligible elders, within designated zip code areas, were contacted. To be eligible, participants had to report no difficulty with activities of daily living, walking a quarter of a mile, or climbing 10 steps without resting. They also had to be free of life-threatening cancer diagnoses and have no plans to move out of the study area for at least 3 years. **Exclusion criteria:** Difficulty with activities	**Method of assessing risk factor/exposure 1:** Self-report Direct measurement Medical record Other – use of medication **Risk factor/exposure 2:** Hypertension **Method of assessing risk factor/exposure 2:** Self-report Direct measurement Medical record Other – use of medication **Risk factor/exposure 3:** Depression **Method of assessing risk factor/exposure 3:** Other- use of CES-D 20 item **Risk factor/exposure 4:** Physical activity **Method of assessing risk factor/exposure 4:** Self-report	'major decliners' older, more black, less educated, lower reading level, lower perceived social support, more likely to live with someone, lower self rated health, fewer drinkers, fewer exercisers, more smokers, more depressed, heavier, more HTN, more DM, more MIs, more CVAs, more e4s, higher il-6, lower triglycerides, higher fasting glc **3) Outcome of interest #1** In the multivariate model, baseline variables significantly associated with being a **Maintainer vs a minor decliner** were: age OR = 0.65, (0.55–0.77 per 5 years), white race OR= 1.72, (1.30–2.28), high school education level or greater (OR= 2.75, 95% CI 1.78–4.26), ninth grade literacy level or greater (OR = 4.85, 95% CI 3.00–7.87), weekly moderate/vigorous exercise OR = 1.31, 95% CI 1.06–1.62), and not smoking (OR= 1.84, 95% CI 1.14–2.97). **4) Outcome of interest #2** **Minor vs Major Decliner** APOE4 OR 2.31 (1.75-3.05) Education ≥12 OR 0.52 (.37-.72) 9th grade literacy or greater OR 0.7 (0.5-.98) Not statistically significant: Htn, DM, drinking 1 alcoholic beverage/day CESD<16, not a current smoker. **5) Outcomes of interest #3** There is a table of all factors	major cognitive decline.
Health ABC	**Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2509 **Duration of follow up:** 8 years **Time from risk factor assessment to final cognitive assessment:** 3, 5 and 7 years				**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? No 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		of daily living, be unable to walk a quarter of a mile, or climb 10 steps without resting. Have life-threatening cancer diagnoses or have plans to move out of the study area for at least 3 years.	**Risk factor/exposure 5:** Smoking **Method of assessing risk factor/exposure 5:** Self-report **Risk factor/exposure 6:** works or volunteers **Method of assessing risk factor/exposure 6:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Race Educational level APOE genotype **Method(s) of assessing cognitive status:** 3MS The participant-specific slopes of 3MS scores were estimated by best linear unbiased predictions using a linear mixed model with random intercepts and slopes. Participants with predicted slopes	adjusted for all others for maintainer vs minor decliner and for major vs minor decliner. For htn OR 1.03 (0.83-1.28) and 1.29(0.97-1.73) Educ (self report) ≥ high school 2.75 (1.78-4.26) 0.52 (0.37-0.73) works or volunteers (self rpt) 1.24 (0.99-1.54) 0.96 (0.73-1.25) has enough social support 0.94 (0.73-1.21) 0.69 (0.51-0.91) drinks >1 etoh daily 1.33 (0.91-1.93) 0.67(0.36-127) moderate to vigorous exercise (>once a week) 1.31 (1.06-1.62) 0.97 (0.73-1.28) not current smoker 1.84 (1.14-2.97) 1.15 (0.72-1.84) ces-d < 16 1.23 (0.68-2.22) 0.70 (0.38-1.29) dm (self rpt OR use of meds OR fasting glc > 126 OR 2 hour challenge glc > 200) 0.91 (0.64-1.30)	

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			of 0 or greater (indicating no change or improvement in cognitive scores over time) were classified as maintainers. Those with predicted slopes less than 0 (decline in cognitive score over time) but no more than one SD below the mean of the slopes were classified as minor decliners. Those with predicted slopes more than 1 SD below the mean were classified as major decliners. **Informant interview?:** No	1.35 (0.92 – 2.00)	
Yaffe, Kanaya, Lindquist, et al., 2004 Health, Aging and Body Composition (ABC) study	**Geographical location:** Memphis, TN and Pittsburgh, PA **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 2632 38.6% of participants with metabolic	**Age:** Mean (SD): 73.6 (2.9) **Sex:** [n (%)] Female: 52 Male: 48 **Race/ethnicity:** [n (%)] 60% white 40% black **Baseline cognitive status:** Non-demented **Inclusion criteria:**	**Risk factor/exposure 1:** Metabolic syndrome defined by National Cholesterol Education Program 3rd Adult treatment panel guidelines (NCEP-ATPIII). At least 3 of the following: 1. Waist measurement (>88cm women; 102cm men). 2. Hypertriglyceridemia (≥150mg/dL (≥1.69 mmmol/L)) 3. Low HDL (men <40mg/dL (<1.03	**1) Follow-up rate:** 2632/2949= 89% 164 died, 69 lost to follow-up, 84 no repeat cognitive testing. **2) Important baseline differences:** Participants with Metabolic syndrome were more likely to be women, white, smoke, higher depression scores, higher BMI, + hx of MI, use statins and NSAIDs, and to have high markers of inflammation. **3) Outcome of interest #1** Cognitive impairment was defined as a change of 5 or more points at	**Comments:** Findings support the hypothesis that metabolic syndrome contributes to cognitive impairment. A primary contributor to cognitive impairment due to metabolic syndrome appears to be inflammation. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5%

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	syndrome. 61.4% without metabolic syndrome. **Duration of follow up:** 5 years **Time from risk factor assessment to final cognitive assessment:** Metabolic syndrome assessed at baseline. Final assessment at 5 years	Random sample of 70 - 79 year old, Medicare eligible whites and blacks living in designated zip codes. Had to be well-functioning (self report of no difficulty in walking ¼ mile or climbing 10 steps without resting.) **Exclusion criteria:** Any difficulty with ADLs, clinical dementia (DSM IV dx), inability to communicate with interviewer, intention of moving out of vicinity in next year, active rx for cancer in prior 3 years, participation in a trial involving a lifestyle intervention. Subjects missing data on metabolic, inflammatory markers, or cognitive testing.	mmol/L)); women (<50mg/dL (<1.29 mmol/L)). 4. High blood pressure (systolic ≥130 mm Hg; diastolic ≥85 mm Hg). 5. High fasting glucose (≥110 mg/dL (≥6.10 mmol/L)) or currently using antidiabetic medication (insulin or oral agents) **Method of assessing risk factor/exposure 1:** Self-report Direct measurement **Risk factor/exposure 2:** inflammatory markers (Interleukin 6 (IL-6) and C-reactive protein (CRP) **Method of assessing risk factor/exposure 2:** Direct measurement **Covariates/potential confounders adjusted for in analyses:** Age Race Sex Educational level Smoking (current) Alcohol use (past year) Baseline cognitive status	either follow-up visit on 3MS. 26% participants with metabolic sx and 21% no metabolic sx. Multivariate adjusted RR 1.66 (95% CI 1.02-1.41) **4) Outcome of interest #2** Individuals with Metabolic sx and high inflammation had increased likelihood of cognitive impairment (RR multivariate adjusted 1.66 (95% CI 1.19-2.32). Individuals with Metabolic syndrome and low inflammation did not have increased risk of cognitive impairment (RR multivariate adjusted 1.08 (95% CI 0.89-1.30) **5) Outcome of interest #3** Stratified multivariate random effects models showed that participants with metabolic sx and high inflammation had greater 4-year decline on 3MS compared to no Met sx (P=.04). Those with metabolic sx and low inflammation did not have greater decline (P=.44)	difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Method(s) of assessing cognitive status: 3MSE **Informant interview?:** No		
Yasar, Corrada, Brookmeyer, et al., 2005 BLSA	**Geographical location:** USA, majority from Baltimore, MD – Washington, D.C. area **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 1092 **Duration of follow up:** Mean yrs 11.0 Range 0.3 – 19.6 **Time from risk factor assessment to final cognitive assessment:** Ongoing assessment of meds throughout study. Some analyses required 2 to 4 year lag time between exposure and final cognitive outcome.	**Age:** Mean (SD): at last f/u 78.1 Range: 61.1 – 104.2 **Sex:** Female: 407 (37.3%) Male: 685 (62.7%) **Race/ethnicity:** [n (%)] White (93%) Other (7%) **Baseline cognitive status:** Non-demented **Inclusion criteria:** Participant in the Baltimore Longitudinal Study of Aging (BLSA > 60 years **Exclusion criteria:** NR	**Risk factor/exposure 1:** antihypertensives (ca channel blocker) **Method of assessing risk factor/exposure 1:** 1980 -1990 self report for past two years, 1990 on pill bottle check **Covariates/potential confounders adjusted for in analyses:** Age, Sex Educational level Smoking, bp, hx heart problems **Method(s) of assessing cognitive status:** NINCDS-ADRDA DSM **Informant interview?:** Yes	**1) Follow-up rate:** NR **2) Important baseline differences:** baseline differences for ad versus not given, but not calcium channel blockers vs not. **3) Outcome of interest #1** RR for any CCB compared to non users 0.63 (0.31 – 1.28) for 2 yr lag 0.71 (0.33 – 1.51) for 4 yr lag **4) Outcome of interest #2** dhp-ccb user vs non user 0.30 (0.07 – 1.25) for 2 yr 0.45 (0.11 – 1.87) for 4 yr lag **5) Outcome of interest #3** non dhp –ccb user vs non user 0.82 (0.37 – 1.83) for 2 yr lag 0.82 (0.35 – 1.95) for 4 yr lag	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Partial 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell, but this appears to be secondary analyses so likely did not significantly influence results 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
Yesavage, Friedman, Ashford, et al., 2008 *(Donepezil)*	**Geographical location:** Palo Alto, USA **Setting:** Community **Study design:** RCT **Test intervention** Donepezil 5mg daily * 6 weeks, then 10mg daily for 46 weeks; dose reduction to 5mg allowed + 2 weeks cognitive training at weeks 13-14 **Comparator intervention(s):** Placebo + 2 weeks cognitive training at weeks 13-14 **Number of participants enrolled:** 168 (83 donepezil; 85 placebo) **Duration of follow up:** 1 year	**Age:** Mean (SD): 65.0 (7.4) donepezil; 64.3 (8.0) placebo **Sex:** [n (%)] Female: 88 Male: 80 **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Normal-71% of participants MCI-29% of participants MMSE 28.6 (1.4) donepezil; 28.6 (1.2) placebo **Inclusion criteria:** Age 55-90 Good general health with normal B12, BP, thyroid, CBC, chemistries MMSE 24-30 Adequate auditory and visual acuity for neuropsych testing **Exclusion criteria:** Hachinski score >4 Hamilton depression rating scale -17 score >12 Significant neurological	**Risk factor/exposure 1:** Cognitive training: Provided to both groups. 2 hours daily * 10 days; visualization techniques and mnemonic training **Method(s) of assessing cognitive status:** Primary: Word list recall at 5 and 30 minutes Name-face recall Secondary: Logical Memory I score Logical Memory II score Symbol digit Digit Span Quality of life (Medical Outcomes Study Functioning and Well-Being Profile) Functional capacity (Everday problems test)	**1) Follow-up rate:** Not given; random regression analysis used ITT principle Adherence: 89% of participants attended all 10 cognitive training sessions **2) Important baseline differences:** More MCI APOE e4 carriers in placebo group (50% vs. 30%) **3) Outcome of interest #1** No significant effects at any timepoint (baseline, week 13 pre-cognitive training, week 14 post-cognitive training, or week 52) Mean change (SD) from baseline at week 52 [positive numbers = improvement] Word list recall: Donepezil 4.5 (4.0) Placebo 4.3 (4.2) Name-face: Donepezil 1.2 (2.7) Placebo 1.6 (2.7) **4) Outcome of interest #2** No significant differences in symbol digit or digit span; logical memory scores not reported No significant differences in quality of life measure or functional capacity **5) Outcome of interest #3**	**Comments:** No power calculation No participant flow (CONSORT) diagram presented No data on medication adherence given **Quality assessment:** *For RCTs:* 1) Baseline comparability? Yes except more APOE carriers in placebo group 2) Valid AD/cognitive outcomes assessment? Yes 3) Subjects/providers blind? Yes 4) Outcome assessors blind? Yes 5) Incomplete data adequately addressed?: Yes 6) Differential dropout rate < 10%? Can't Tell 7) Overall dropout rate < 30%? Can't Tell 8) Conflict of interest reported and insignificant? No, NIMH and VA funded 9) Randomization adequate? Yes 10) Allocation concealment adequate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		disease (other than suspected incipient AD) MDD, Alcohol or substance dependence in the past 2 years		Dropouts for any reason in first 12 weeks: 15/83 (18.0%) donepezil vs. 6/85 (7.1%), p<0.05 Most common Adverse events: Donepezil vs. Placebo Muscle cramps: 19 vs. 1 Insomnia: 18 vs. 8 Abnormal dreams: 12 vs. 6 Nausea: 7 vs. 2 Only muscle cramps and insomnia statistically significant	
Yoshitake, Kiyohara, Kato, et al., 1995 The Hisayama Study	**Geographical location:** Hisayama Town, Japan **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 828 **Duration of follow up:** Seven years **Time from risk factor assessment to final cognitive assessment:** 7 years	**Age:** Mean (SD): For men: 73 (5.6) For women: 74 (6.1) **Sex:** [n (%)] Female: 494 (60%) Male: 334 (40%) **Race/ethnicity:** Japanese: 100% **Baseline cognitive status:** Non-demented **Inclusion criteria:** Resident of Hisayama Town Age ≥ 65 years **Exclusion criteria:** Demented	**Risk factor/exposure 1:** physical activity **Method of assessing risk factor/exposure 1:** Self-report "we defined the physically active group as those including daily exercise during the leisure period or moderate to severe physical activity at work." **Covariates/potential confounders adjusted for in analyses:** [delete any from the list below that do not apply and add items as needed] Age	**1) Follow-up rate:** Initially 828. 214 died during f/u. f/u: 577 of 614 survivors (94.0%); 577 or 828 recruited (70%) **2) Important baseline differences:** NR **3) Outcome of interest #1--AD** "Age and a low score on Hasegawa's dementia scale were significant risk factors for AD, and physical activity was a significant preventive factor." RR (95% CI) Physically active: 0.20 (0.06-0.68)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Can't Tell 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? No, measure not cited and no validation 6) Validated method for ascertaining clinical outcomes? Can't Tell 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Sex **Method(s) of assessing cognitive status:** [delete all that do not apply] 2-stage assessment; second stage based on clinical evaluation but assessment not well specified NINCDS-ADRDA DSM **Informant interview?:** No		confounding? Partial 11) Analytic methods appropriate? Yes
Yu, Ryan, Schaie, et al., 2009 Seattle Longitudinal Study SLS	**Geographical location:** Pacific Northwest USA **Setting:** Other – health maintenance organization (HMO) **Study design:** Prospective cohort **Number of participants enrolled:** 626 **Duration of follow up:** 14 yrs **Time from risk factor assessment to final cognitive assessment:**	**Age:** Mean (SD): 53.20 (12.76) Range: 23 – 82 **Sex:** [n (%)] Female: 351 (56%) Male: 275 (44%) **Race/ethnicity:** [n (%)] White 601 (96%) Other 25 (4%) **Baseline cognitive status:** No exclusion based on cognitive status. 429 of the 502 participants over 60 years of age were given the neuropsychological battery. Of those, 3.7% were identified as	**Risk factor/exposure 1**: leisure-time physical activity, leisure-time cognitive activity **Method of assessing risk factor/exposure 1**: Self-report survey: Life Complexity Inventory, LCI **Risk factor/exposure 2:** self-directed work, (work control, perceived autonomy and innovation) **Method of assessing risk factor/exposure 2**:	**1) Follow-up rate:** 703 participants initially, 77 participants had missing data, so final sample of 626 participants, representing 38% of the total SLS sample in1984 (n= 1,647). Average yearly attrition rate for the study sample was 2.71%. **2) Important baseline differences:** Compared to the SLS total sample in 1984, the study sample was younger, but otherwise relatively equivalent **2) Outcome of interest #1** Work control was the only significant factor associated with verbal memory ($p<0.05$) **3) Outcome of interest #2** Work control was the only significant factor associated with inductive	**Comments:** This study did not exclude participants who may have been impaired at the beginning of the study though the mean age of the cohort was 53 at entry. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Partial 2) Selection minimizes baseline differences in prognostic factors? Partial 3) Sample size calculated/5% difference? No 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Yes 6) Validated method for ascertaining clinical outcomes? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
	14 years	having probable or definite dementia in 1998, representing 2.2% of the sample **Inclusion criteria:** SLS participants who met two criteria: (a) had completed three waves of data collection (in 1984, 1991, and 1998) (b) had no missing data for the independent variables and covariates **Exclusion criteria:** NR	Self-report Work Environment Inventory **Risk Factor/Exposure: 3.** Hypertension **Method of assessing risk factor/exposure 3:** The diagnosis was retrieved from participants' HMO records **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Income **Method(s) of assessing cognitive status:** Other – [specify] Verbal memory (a) word fluency (b) immediate recall (c)delayed recall Inductive reasoning (a) Primary Mental Abilities, PMA, reasoning measure (b) Adult Development and Enrichment Project letter series,	reasoning. Every increased unit of work control at the third wave was associated with a .14 t-score unit increase in inductive reasoning ($p<0.05$)	7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Can't Tell 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			ADEPT-letter (c) word series and (d) Educational Testing Service number series **Informant interview?:** No		
Zandi, Sparks, Khachaturian, et al., 2005 Cache County Study	**Geographical location:** Cache County, UT **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 4895 **Duration of follow up:** 3 yrs **Time from risk factor assessment to final cognitive assessment:** 3 yrs	**Age:** Mean (SD): 73.0 to 75.7 **Sex:** Female: 2797 (57%) Male: 2098 (43%) **Race/ethnicity:** NR **Baseline cognitive status:** Non-demented **Inclusion criteria:** ≥ 65 yo; permanent resident of Cache County, UT **Exclusion criteria:** Less than 65 years old Resident outside of Cache County, UT Dementia at baseline	**Risk factor/exposure 1:** Statin **Method of assessing risk factor/exposure 1:** Direct measurement – medication bottles Medical record - supplemented **Risk factor/exposure 2:** education; h/o stroke; HTN or DM; smoking **Method of assessing risk factor/exposure 2:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level Number of ApoE E4 alleles,	**1) Follow-up rate:** 3308/4540 (82.8%) 508 died 724 lost to f/u HR (95% CI) for AD – unadjusted Statin used 4AD/630 person years, HR 0.62 (0.19 to 1.48) No statin used 98/9522 person years, HR 1.0 (ref) Statin <= 3 years HR 0.49 (0.08 to 1.54) Statin > 3 years 0.43 (0.03 to 1.96) HR (95% CI) for AD – adjusted for age, sex, education, number o Apoe e4 alleles, age by e4 interaction, h/o HTN, h/o DM Statin used 4AD/630 person years, HR 1.19 (0.35 to 2.96) No statin used 98/9522 person years, HR 1.0 (ref) Statin <= 3 years HR 1.41 (0.23 to 4.70) Statin > 3 years 0.62 (0.03 to 2.92)	**Comments:** None **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Yes, Post-hoc 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Yes 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Yes 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			age X e4 interaction h/o diabetes h/o hypertension **Method(s) of assessing cognitive status:** Other – Screen with modified 3MS or IQCODE. High risk by screening or clinical characteristics underwent detailed history, examination and neuropsych testing. NINCDS-ADRDA **Informant interview?:** Yes Text in the article reports that informant interviews were included when participants could not do 3MS.		
Zandi, Anthony, Hayden, et al., 2002 Cache	**Geographical location:** Cache County Utah. **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 3511, 104 AD	**Age:** Range: 65 years and up **Sex:** [n (%)] Female: NR Male: NR **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:**	**Risk factor/exposure 1:** nsaids **Method of assessing risk factor/exposure 1:** Self-report And examination of pill bottles **Covariates/potential confounders**	**1) Follow-up rate:** 83% of those without baseline dementia and still alive. **2) Important baseline differences:** non asa nsaid users more likely to be women. **3) Outcome of interest #1** Use of nsaids for > 2 years associated with decreased risk of ad (but not current use unless use extended for 2 years prior to wave 1).	**Comments:** Question 1 waves 1 and 3 of Cache. **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? No

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		Normal	**adjusted for in analyses:**	Hr	4) Adequate description of the cohort? Yes
	Duration of follow up: 3 years	Non-demented	Age, squared deviation of age,Sex,apoe4, interaction age/apoE4 Educational level Baseline cognitive status	0.45 (0.17-0.97)	5) Validated method for ascertaining exposure? Yes
	Time from risk factor assessment to final cognitive assessment: 3 years	**Inclusion criteria:** Participating in the Cache County Study		**4) Outcome of interest #2** Any lifetime use of nsaids almost associated with decreased risk of ad with hr 0.67 (o,40-1.06)	6) Validated method for ascertaining clinical outcomes? Yes
		Exclusion criteria: Less than 65 years old	**Method(s) of assessing cognitive status:** DSM		7) Outcome assessment blind to exposure? Yes
					8) Adequate follow-up period? Yes
			Informant interview?: sometimes		9) Completeness of follow-up? Yes
					10) Analysis controls for confounding? Yes
					11) Analytic methods appropriate? Yes
Zandi, Anthony, Khachaturian, et al., 2004 Cache County Study	**Geographical location:** Logan, UT, USA	**Age:** Mean (SD): mean range across exposure categories: 74.2-76.6	**Risk factor/exposure 1:** Vitamins E and C, multivitamins, B-complex vitamins	**1) Follow-up rate:** 3227/ 4110 (denominator excludes those lost to f/u due to death)	**Comments:** Question 1
	Setting: Community	**Sex:** [n (%)] Female: mean % range across exposure categories: 53.6-64.0	**Method of assessing risk factor/exposure 1:** Self-report	**2) Important baseline differences:** User of Vitamin C or E were more likely to be female, younger, better educated and report better general health	**Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes
	Study design: Prospective cohort	**Race/ethnicity:** [n (%)] NR	**Covariates/potential confounders adjusted for in analyses:** Age Sex Educational level APOE General health status	**3) Outcome of interest #1** Reduced risk of incident AD associated with combined Vitamin E and C use (HR=0.36; 0.09-0.99)	2) Selection minimizes baseline differences in prognostic factors? Yes
	Number of participants enrolled: 3227	**Baseline cognitive status:** Non-demented		No significant association between incident AD and Vitamin E alone, Vitamin C alone, multivitamin, or B-complex vitamins or any combination of these except for Vitamin E and C combined	3) Sample size calculated/5% difference? Can't Tell
	Duration of follow up: Est 3 yr	**Inclusion criteria:** Resident of Cache County, UT; age ≥ 65 yrs			4) Adequate description of the cohort? Yes
	Time from risk factor assessment to final cognitive assessment: Est 3 yr				5) Validated method for ascertaining exposure? Yes
		Exclusion criteria:	**Method(s) of assessing cognitive**		6) Validated method for ascertaining clinical outcomes? Yes
					7) Outcome assessment blind to exposure? Yes
					8) Adequate follow-up period? Yes
					9) Completeness of follow-up? Yes

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
		None	**status:** NINCDS-ADRDA DSM-3 revised **Informant interview?:** Yes		10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes
Zunzunegui, Alvarado, Del Ser, et al., 2003	**Geographical location:** Leganes, a suburb of Madrid, Spain **Setting:** Community **Study design:** Prospective cohort **Number of participants enrolled:** 557 analytical sample **Duration of follow up:** 4 yrs **Time from risk factor assessment to final cognitive assessment:** 4 yrs	**Age:** Mean (SD): NR **Sex:** [n (%)] Female: 264 (47.3) Male: 293 (52.7) **Race/ethnicity:** [n (%)] NR **Baseline cognitive status:** Non-demented (excluded individuals thought to be severely impaired based on cognitive screening score) **Inclusion criteria:** Stratified random sample of common-dwelling residents of Leganes, Spain > 65 years **Exclusion criteria:** Severely cognitively impaired defined as $\geq$ 5 errors on the SPMSQ, visually impaired	**Risk factor/exposure 1:** Social networks (number of monthly visual and phone contacts with friends and relatives (other than children)), social integration (membership in community associations, monthly attendance of religious services, visits to the community center) and social engagement (how frequently help, are useful, and play important roll in life of children, family and friends) **Method of assessing risk factor/exposure 1:** Self-report **Covariates/potential confounders adjusted for in analyses:** Age Educational level	**1) Follow-up rate:** 557/964 completed f/u. 152 of the 964 were deceased, so f/u rate 557/812 (69%). **2) Important baseline differences:** Men were more likely to be married whereas women were more likely to live alone or with family. Women reported less extensive networks than men. Attendance of religious services occurred more frequently among women than men. Women tended to be less engaged with friends than men. There were more women reporting cardiovascular morbidity (51.0%), high depressive symptomatology (40.5%), and functional limitations (22.7%), than men (36.0%, $p < .001$; 12.0%, $p < .001$; 8.0%, $p < .001$, respectively). There were no significant gender differences with respect to frequency of cognitive decline: 10.5% of women had severe and 24.6% mild decline, whereas 12.9% of men showed severe and 18.5% mild decline. **3) Outcome of interest #1** Increased risk of severe decline was only associated with no group membership in men, less social engagement with children in men,	**Comments:** Q2 – yes cat Dx **Quality assessment:** *For observational studies:* 1) Unbiased selection of the cohort? Yes 2) Selection minimizes baseline differences in prognostic factors? Yes 3) Sample size calculated/5% difference? Can't Tell 4) Adequate description of the cohort? Yes 5) Validated method for ascertaining exposure? Partial 6) Validated method for ascertaining clinical outcomes? Yes 7) Outcome assessment blind to exposure? Can't Tell 8) Adequate follow-up period? Yes 9) Completeness of follow-up? Partial 10) Analysis controls for confounding? Yes 11) Analytic methods appropriate? Yes (but limited description of how to interpret results makes interpreting results difficult)

Study	Study Information	Participants	Risk Factor and Outcome Assessment	Results	Comments/Quality Scoring
			Sex Baseline cognitive status Depression Blood pressure Functional limitations **Method(s) of assessing cognitive status:** Other – decline on composite measure of cognitive tests. Severe decline defined as greater than 1 SD below the mean change. Mild decline defined as a change within 1 SD of the mean change. **Informant interview?:** No	and less social engagement with friends in women. **4) Outcome of interest #2** The number of relatives seen at least monthly (p = 0.028) and the social integration index (p = 0.04) are significant predictors of cognitive decline for both sexes. Among women, engagement with friends predicts lower probability of cognitive decline. (interaction p= 0.19). Neither engagement with relatives or children was related to decline in this final model. Depression is associated with decline in men but not in women. (interaction p = 0.051).	

Articles Included in the Evidence Tables (in Alphabetical Order)

Aartsen MJ, Van Tilburg T, Smits CH, et al. Does widowhood affect memory performance of older persons? Psychol Med 2005;35(2):217-26.

Abbott RD, White LR, Ross GW, et al. Walking and dementia in physically capable elderly men. JAMA 2004;292(12):1447-53.

Adapt Research Group, Lyketsos CG, Breitner JC, et al. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. Neurology 2007;68(21):1800-8.

Aggarwal NT, Bienias JL, Bennett DA, et al. The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. Neuroepidemiology 2006;26(3):140-6.

Akbaraly TN, Hininger-Favier I, Carriere I, et al. Plasma selenium over time and cognitive decline in the elderly. Epidemiology 2007;18(1):52-8.

Akbaraly TN, Portet F, Fustinoni S, et al. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology 2009;73(11):854-61.

Akomolafe A, Beiser A, Meigs JB, et al. Diabetes mellitus and risk of developing Alzheimer disease: results from the Framingham Study. Arch Neurol 2006;63(11):1551-5.

Alvarado BE, Zunzunegui MV, Del Ser T, et al. Cognitive decline is related to education and occupation in a Spanish elderly cohort. Aging Clin Exp Res 2002;14(2):132-42.

Alves de Moraes S, Szklo M, Knopman D, et al. The relationship between temporal changes in blood pressure and changes in cognitive function: atherosclerosis risk in communities (ARIC) study. Prev Med 2002;35(3):258-63.

Andel R, Crowe M, Pedersen NL, et al. Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins. J Gerontol A Biol Sci Med Sci 2008;63(1):62-6.

Anonymous. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. [summary for patients in Curr Cardiol Rep. 2002 Nov;4(6):486-7; PMID: 12379169]. Lancet 2002;360(9326):7-22.

Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch Intern Med 1994;154(19):2154-60.

Arvanitakis Z, Grodstein F, Bienias JL, et al. Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology. Neurology 2008;70(23):2219-25.

Arvanitakis Z, Schneider J, Wilson R, et al. Statins, incident Alzheimer disease, change in cognitive function, and neuropathology. Neurology 2008;70(19 Pt 2):1795-802.

Atti AR, Palmer K, Volpato S, et al. Late-life body mass index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. J Am Geriatr Soc 2008;56(1):111-6.

Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA 2002;288(18):2271-81.

Barnes DE, Alexopoulos GS, Lopez OL, et al. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. Arch Gen Psychiatry 2006;63(3):273-9.

Barnes DE, Cauley JA, Lui LY, et al. Women who maintain optimal cognitive function into old age. J Am Geriatr Soc 2007;55(2):259-64.

Barnes LL, Mendes de Leon CF, Wilson RS, et al. Social resources and cognitive decline in a population of older African Americans and whites. Neurology 2004;63(12):2322-6.

Bernick C, Katz R, Smith N, et al. Statins and cognitive function in the elderly: the Cardiovascular Health Study. Neurology 2005;65(9):1388-94.

Berr C, Balansard B, Arnaud J, et al. Cognitive decline is associated with systemic oxidative stress: the EVA study. Etude du Vieillissement Arteriel. J Am Geriatr Soc 2000;48(10):1285-91.

Beydoun MA, Kaufman JS, Satia JA, et al. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr 2007;85(4):1103-11.

Beydoun MA, Kaufman JS, Sloane PD, et al. n-3 Fatty acids, hypertension and risk of cognitive decline among older adults in the Atherosclerosis Risk in Communities (ARIC) study. Public Health Nutr 2008;11(1):17-29.

Bierman EJ, Comijs HC, Rijmen F, et al. Anxiety symptoms and cognitive performance in later life: results from the longitudinal aging study Amsterdam. Aging Ment Health 2008;12(4):517-23.

Blair CK, Folsom AR, Knopman DS, et al. APOE genotype and cognitive decline in a middle-aged cohort. Neurology 2005;64(2):268-76.

Blasko I, Jellinger K, Kemmler G, et al. Conversion from cognitive health to mild cognitive impairment and Alzheimer's disease: prediction by plasma amyloid beta 42, medial temporal lobe atrophy and homocysteine. Neurobiol Aging 2008;29(1):1-11.

Borenstein AR, Wu Y, Mortimer JA, et al. Developmental and vascular risk factors for Alzheimer's disease. Neurobiol Aging 2005;26(3):325-34.

Bosma H, van Boxtel MP, Ponds RW, et al. Engaged lifestyle and cognitive function in middle and old-aged, non-demented persons: a reciprocal association? Z Gerontol Geriatr 2002;35(6):575-81.

Breitner JC, Haneuse SJ, Walker R, et al. Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. Neurology 2009;72(22):1899-905.

Bretsky P, Guralnik JM, Launer L, et al. The role of APOE-epsilon4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. Neurology 2003;60(7):1077-81.

Carmelli D, Swan GE, Reed T, et al. Midlife cardiovascular risk factors, ApoE, and cognitive decline in elderly male twins. Neurology 1998;50(6):1580-5.

Cherbuin N, Reglade-Meslin C, Kumar R, et al. Risk factors of transition from normal cognition to mild cognitive disorder: the PATH through Life Study. Dement Geriatr Cogn Disord 2009;28(1):47-55.

Christensen H, Batterham PJ, Mackinnon AJ, et al. The association of APOE genotype and cognitive decline in interaction with risk factors in a 65-69 year old community sample. BMC Geriatr 2008;8:14.

Christensen H, Henderson AS, Korten AE, et al. ICD-10 mild cognitive disorder: its outcome three years later. Int J Geriatr Psychiatry 1997;12(5):581-6.

Clarke R, Birks J, Nexo E, et al. Low vitamin B-12 status and risk of cognitive decline in older adults. Am J Clin Nutr 2007;86(5):1384-91.

Comijs HC, Kriegsman DM, Dik MG, et al. Somatic chronic diseases and 6-year change in cognitive functioning among older persons. Arch Gerontol Geriatr 2009;48(2):191-6.

Commenges D, Scotet V, Renaud S, et al. Intake of flavonoids and risk of dementia. Eur J Epidemiol 2000;16(4):357-63.

Cornelius C, Fastbom J, Winblad B, et al. Aspirin, NSAIDs, risk of dementia, and influence of the apolipoprotein E epsilon 4 allele in an elderly population. Neuroepidemiology 2004;23(3):135-43.

Dai Q, Borenstein AR, Wu Y, et al. Fruit and vegetable juices and Alzheimer's disease: the Kame Project. Am J Med 2006;119(9):751-9.

de Lau LM, Smith AD, Refsum H, et al. Plasma vitamin B12 status and cerebral white-matter lesions. J Neurol Neurosurg Psychiatry 2009;80(2):149-57.

DeKosky ST, Williamson JD, Fitzpatrick AL, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA 2008;300(19):2253-62.

Devore EE, Grodstein F, van Rooij FJ, et al. Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. Am J Clin Nutr 2009;90(1):170-6.

Devore EE, Kang JH, Okereke O, et al. Physical activity levels and cognition in women with type 2 diabetes. Am J Epidemiol 2009;170(8):1040-7.

Dik MG, Jonker C, Bouter LM, et al. APOE-epsilon4 is associated with memory decline in cognitively impaired elderly. Neurology 2000;54(7):1492-7.

Dodge HH, Zitzelberger T, Oken BS, et al. A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. Neurology 2008;70(19 Pt 2):1809-17.

Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurology 2009;72(18):1555-61.

Dufouil C, Alperovitch A, Ducros V, et al. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. Ann Neurol 2003;53(2):214-21.

Dufouil C, Fuhrer R, Dartigues JF, et al. Longitudinal analysis of the association between depressive symptomatology and cognitive deterioration. Am J Epidemiol 1996;144(7):634-41.

Dullemeijer C, Durga J, Brouwer IA, et al. n 3 fatty acid proportions in plasma and cognitive performance in older adults. Am J Clin Nutr 2007;86(5):1479-85.

Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 2002;287(24):3223-9.

Evans DA, Hebert LE, Beckett LA, et al. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. Arch Neurol 1997;54(11):1399-405.

Everson-Rose SA, Mendes de Leon CF, Bienias JL, et al. Early life conditions and cognitive functioning in later life. Am J Epidemiol 2003;158(11):1083-9.

Feart C, Samieri C, Rondeau V, et al. Adherence to a Mediterranean diet, cognitive

decline, and risk of dementia. JAMA 2009;302(6):638-48.

Fillenbaum GG, Kuchibhatla MN, Hanlon JT, et al. Dementia and Alzheimer's disease in community-dwelling elders taking vitamin C and/or vitamin E. Ann Pharmacother 2005;39(12):2009-14.

Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol 2009;66(3):336-42.

Fotuhi M, Zandi PP, Hayden KM, et al. Better cognitive performance in elderly taking antioxidant vitamins E and C supplements in combination with nonsteroidal anti-inflammatory drugs: the Cache County Study. Alzheimers Dement 2008;4(3):223-7.

Fratiglioni L, Wang HX, Ericsson K, et al. Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000;355(9212):1315-9.

Freitag MH, Peila R, Masaki K, et al. Midlife pulse pressure and incidence of dementia: the Honolulu-Asia Aging Study. Stroke 2006;37(1):33-7.

Gallacher J, Bayer A, Fish M, et al. Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study. Psychosom Med 2009;71(6):659-66.

Gatz JL, Tyas SL, St John P, et al. Do depressive symptoms predict Alzheimer's disease and dementia? J Gerontol A Biol Sci Med Sci 2005;60(6):744-7.

Geda YE, Knopman DS, Mrazek DA, et al. Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: a prospective cohort study. Arch Neurol 2006;63(3):435-40.

Geerlings MI, den Heijer T, Koudstaal PJ, et al. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. Neurology 2008;70(15):1258-64.

Glynn RJ, Beckett LA, Hebert LE, et al. Current and remote blood pressure and cognitive decline. JAMA 1999;281(5):438-45.

Gonzalez HM, Bowen ME, Fisher GG. Memory decline and depressive symptoms in a nationally representative sample of older adults: the Health and Retirement Study (1998-2004). Dement Geriatr Cogn Disord 2008;25(3):266-71.

Graves AB, Rajaram L, Bowen JD, et al. Cognitive decline and Japanese culture in a cohort of older Japanese Americans in King County, WA: the Kame Project. J Gerontol B Psychol Sci Soc Sci 1999;54(3):S154-61.

Gray SL, Anderson ML, Crane PK, et al. Antioxidant vitamin supplement use and risk of dementia or Alzheimer's disease in older adults. J Am Geriatr Soc 2008;56(2):291-5.

Green AF, Rebok G, Lyketsos CG. Influence of social network characteristics on cognition and functional status with aging. Int J Geriatr Psychiatry 2008;23(9):972-8.

Grodstein F, Skarupski KA, Bienias JL, et al. Anti-inflammatory agents and cognitive decline in a bi-racial population. Neuroepidemiology 2008;30(1):45-50.

Guo Z, Fratiglioni L, Viitanen M, et al. Apolipoprotein E genotypes and the incidence of Alzheimer's disease among persons aged 75 years and older: variation by use of antihypertensive medication? Am J Epidemiol 2001;153(3):225-31.

Haag M, Hofman A, Koudstaal P, et al. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. J Neurol Neurosurg Psychiatry 2009;80(1):13-7.

Haag MD, Hofman A, Koudstaal PJ, et al. Duration of antihypertensive drug use and risk of dementia: A prospective cohort study. Neurology 2009;72(20):1727-34.

Haan MN, Shemanski L, Jagust WJ, et al. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA 1999;282(1):40-6.

Hakansson K, Rovio S, Helkala EL, et al. Association between mid-life marital status and cognitive function in later life: population based cohort study. BMJ 2009;339:b2462.

Hayden KM, Zandi PP, Khachaturian AS, et al. Does NSAID use modify cognitive trajectories in the elderly? The Cache County study. Neurology 2007;69(3):275-82.

Hebert LE, Scherr PA, Bennett DA, et al. Blood pressure and late-life cognitive function change: a biracial longitudinal population study. Neurology 2004;62(11):2021-4.

Hee Kang J, Cook N, Manson J, et al. Low dose aspirin and cognitive function in the women's health study cognitive cohort. BMJ 2007;334(7601):987.

Hee Kang J, Grodstein F. Regular use of nonsteroidal anti-inflammatory drugs and cognitive function in aging women. Neurology 2003;60(10):1591-7.

Helmer C, Damon D, Letenneur L, et al. Marital status and risk of Alzheimer's disease: a French population-based cohort study. Neurology 1999;53(9):1953-8.

Ho RC, Niti M, Yap KB, et al. Metabolic syndrome and cognitive decline in chinese older adults: results from the singapore longitudinal ageing studies. Am J Geriatr Psychiatry 2008;16(6):519-22.

Ho SC, Woo J, Sham A, et al. A 3-year follow-up study of social, lifestyle and health predictors of cognitive impairment in a Chinese older cohort. Int J Epidemiol

2001;30(6):1389-96.

Holtzman RE, Rebok GW, Saczynski JS, et al. Social network characteristics and cognition in middle-aged and older adults. J Gerontol B Psychol Sci Soc Sci 2004;59(6):P278-84.

Huang TL, Zandi PP, Tucker KL, et al. Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4. Neurology 2005;65(9):1409-14.

Hughes TF, Andel R, Small BJ, et al. Midlife Fruit and Vegetable Consumption and Risk of Dementia in Later Life in Swedish Twins. Am J Geriatr Psychiatry 2009.

Hughes TF, Borenstein AR, Schofield E, et al. Association between late-life body mass index and dementia: The Kame Project. Neurology 2009;72(20):1741-6.

Insel KC, Palmer RF, Stroup-Benham CA, et al. Association between change in systolic blood pressure and cognitive decline among elderly Mexican Americans: data from the Hispanic established population for epidemiology study of the elderly. Exp Aging Res 2005;31(1):35-54.

in't Veld BA, Ruitenberg A, Hofman A, et al. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiol Aging 2001;22(3):407-12.

Irie F, Fitzpatrick AL, Lopez OL, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the Cardiovascular Health Study Cognition Study. Arch Neurol 2008;65(1):89-93.

Irie F, Masaki KH, Petrovitch H, et al. Apolipoprotein E epsilon4 allele genotype and the effect of depressive symptoms on the risk of dementia in men: the Honolulu-Asia Aging Study. Arch Gen Psychiatry 2008;65(8):906-12.

Jonker C, Comijs HC, Smit JH. Does aspirin or other NSAIDs reduce the risk of cognitive decline in elderly persons? Results from a population-based study. Neurobiol Aging 2003;24(4):583-8.

Kado DM, Karlamangla AS, Huang MH, et al. Homocysteine versus the vitamins folate, B6, and B12 as predictors of cognitive function and decline in older high-functioning adults: MacArthur Studies of Successful Aging. Am J Med 2005;118(2):161-7.

Kalmijn S, Feskens EJ, Launer LJ, et al. Longitudinal study of the effect of apolipoprotein e4 allele on the association between education and cognitive decline in elderly men. BMJ 1997;314(7073):34-5.

Kalmijn S, Feskens EJ, Launer LJ, et al. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol 1997;145(1):33-41.

Kalmijn S, Launer LJ, Lindemans J, et al. Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study. Am J Epidemiol 1999;150(3):283-9.

Kalmijn S, Launer LJ, Ott A, et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 1997;42(5):776-82.

Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. Ann Neurol 2005;57(5):713-20.

Kang JH, Cook N, Manson J, et al. A trial of B vitamins and cognitive function among women at high risk of cardiovascular disease. Am J Clin Nutr 2008;88(6):1602-10.

Kang JH, Cook N, Manson J, et al. A randomized trial of vitamin E supplementation and cognitive function in women. Arch Intern Med 2006;166(22):2462-8.

Kang JH, Cook NR, Manson JE, et al. Vitamin E, vitamin C, beta carotene, and cognitive function among women with or at risk of cardiovascular disease: The Women's Antioxidant and Cardiovascular Study. Circulation 2009;119(21):2772-80.

Kang JH, Grodstein F. Plasma carotenoids and tocopherols and cognitive function: a prospective study. Neurobiol Aging 2008;29(9):1394-403.

Karlamangla AS, Miller-Martinez D, Aneshensel CS, et al. Trajectories of cognitive function in late life in the United States: demographic and socioeconomic predictors. Am J Epidemiol 2009;170(3):331-42.

Khachaturian AS, Zandi PP, Lyketsos CG, et al. Antihypertensive medication use and incident Alzheimer disease: the Cache County Study. Arch Neurol 2006;63(5):686-92.

Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 2001;322(7300):1447-51.

Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005;62(10):1556-60.

Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56(1):42-8.

Knopman DS, Mosley TH, Catellier DJ, et al. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. Alzheimers Dement 2009;5(3):207-14.

Koster A, Penninx BW, Bosma H, et al. Socioeconomic differences in cognitive decline and the role of biomedical factors. Ann Epidemiol 2005;15(8):564-71.

Kritz-Silverstein D, von Muhlen D, Laughlin GA, et al. Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. J Am Geriatr Soc 2008;56(7):1292-8.

Kroger E, Verreault R, Carmichael PH, et al. Omega-3 fatty acids and risk of dementia: the Canadian Study of Health and Aging. Am J Clin Nutr 2009;90(1):184-92.

Kuo HK, Jones RN, Milberg WP, et al. Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: a longitudinal analysis of the advanced cognitive training for independent and vital elderly cohort. J Am Geriatr Soc 2005;53(7):1154-61.

Laitinen MH, Ngandu T, Rovio S, et al. Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study. Dement Geriatr Cogn Disord 2006;22(1):99-107.

Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006;144(2):73-81.

Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging 2000;21(1):49-55.

Laurin D, Masaki KH, Foley DJ, et al. Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol 2004;159(10):959-67.

Laurin D, Verreault R, Lindsay J, et al. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 2001;58(3):498-504.

Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 2008;300(9):1027-37.

Lee S, Buring JE, Cook NR, et al. The relation of education and income to cognitive function among professional women. Neuroepidemiology 2006;26(2):93-101.

Lee S, Kawachi I, Berkman LF, et al. Education, other socioeconomic indicators, and cognitive function. Am J Epidemiol 2003;157(8):712-20.

Li G, Higdon R, Kukull WA, et al. Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. Neurology 2004;63(9):1624-8.

Li G, Rhew IC, Shofer JB, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. J Am Geriatr Soc 2007;55(8):1161-7.

Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 2002;156(5):445-53.

Lu PH, Edland SD, Teng E, et al. Donepezil delays progression to AD in MCI subjects with depressive symptoms. Neurology 2009;72(24):2115-21.

Luchsinger JA, Honig LS, Tang MX, et al. Depressive symptoms, vascular risk factors, and Alzheimer's disease. Int J Geriatr Psychiatry 2008;23(9):922-8.

Luchsinger JA, Reitz C, Honig LS, et al. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology 2005;65(4):545-51.

Luchsinger JA, Tang MX, Miller J, et al. Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. Arch Neurol 2007;64(1):86-92.

Luchsinger JA, Tang MX, Shea S, et al. Caloric intake and the risk of Alzheimer disease. Arch Neurol 2002;59(8):1258-63.

Luchsinger JA, Tang MX, Shea S, et al. Antioxidant vitamin intake and risk of Alzheimer disease. Arch Neurol 2003;60(2):203-8.

Luchsinger JA, Tang MX, Shea S, et al. Plasma homocysteine levels and risk of Alzheimer disease. Neurology 2004;62(11):1972-6.

Lytle ME, Vander Bilt J, Pandav RS, et al. Exercise level and cognitive decline: the MoVIES project. Alzheimer Dis Assoc Disord 2004;18(2):57-64.

Manly JJ, Schupf N, Tang MX, et al. Cognitive decline and literacy among ethnically diverse elders. J Geriatr Psychiatry Neurol 2005;18(4):213-7.

Martin BK, Szekely C, Brandt J, et al. Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. Arch Neurol 2008;65(7):896-905.

Masaki KH, Losonczy KG, Izmirlian G, et al. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. Neurology 2000;54(6):1265-72.

Maxwell CJ, Hicks MS, Hogan DB, et al. Supplemental use of antioxidant vitamins and subsequent risk of cognitive decline and dementia. Dement Geriatr Cogn Disord 2005;20(1):45-51.

McMahon JA, Green TJ, Skeaff CM, et al. A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med 2006;354(26):2764-72.

McNeill G, Avenell A, Campbell MK, et al. Effect of multivitamin and multimineral supplementation on cognitive function in men and women aged 65 years and over: a randomised controlled trial. Nutr J 2007;6:10.

Mehta KM, Ott A, Kalmijn S, et al. Head trauma and risk of dementia and Alzheimer's disease: The Rotterdam Study. Neurology 1999;53(9):1959-62.

Morris MC, Beckett LA, Scherr PA, et al. Vitamin E and vitamin C supplement use and risk of incident Alzheimer disease. Alzheimer Dis Assoc Disord 1998;12(3):121-6.

Morris MC, Evans DA, Bienias JL, et al. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. J Neurol Neurosurg Psychiatry 2004;75(8):1093-9.

Morris MC, Evans DA, Bienias JL, et al. Dietary fats and the risk of incident Alzheimer disease. Arch Neurol 2003;60(2):194-200.

Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. JAMA 2002;287(24):3230-7.

Morris MC, Evans DA, Bienias JL, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003;60(7):940-6.

Morris MC, Evans DA, Bienias JL, et al. Dietary folate and vitamin B12 intake and cognitive decline among community-dwelling older persons. Arch Neurol 2005;62(4):641-5.

Morris MC, Evans DA, Bienias JL, et al. Vitamin E and cognitive decline in older persons. Arch Neurol 2002;59(7):1125-32.

Morris MC, Evans DA, Bienias JL, et al. Dietary fat intake and 6-year cognitive change in an older biracial community population. Neurology 2004;62(9):1573-9.

Morris MC, Evans DA, Schneider JA, et al. Dietary folate and vitamins B-12 and B-6 not associated with incident Alzheimer's disease. J Alzheimers Dis 2006;9(4):435-43.

Morris MC, Evans DA, Tangney CC, et al. Dietary copper and high saturated and trans fat intakes associated with cognitive decline. Arch Neurol 2006;63(8):1085-8.

Morris MC, Evans DA, Tangney CC, et al. Associations of vegetable and fruit consumption with age-related cognitive change. Neurology 2006;67(8):1370-6.

Morris MC, Evans DA, Tangney CC, et al. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. Am J Clin Nutr 2005;81(2):508-14.

Morris MC, Scherr PA, Hebert LE, et al. Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. Arch Neurol 2001;58(10):1640-6.

Muller M, Tang MX, Schupf N, et al. Metabolic syndrome and dementia risk in a multiethnic elderly cohort. Dement Geriatr Cogn Disord 2007;24(3):185-92.

Muniz-Terrera G, Matthews F, Dening T, et al. Education and trajectories of cognitive decline over 9 years in very old people: methods and risk analysis. Age Ageing 2009;38(3):277-82.

Ng TP, Niti M, Zaw MH, et al. Depressive symptoms and incident cognitive impairment in cognitively well-functioning older men and women. J Am Geriatr Soc 2009;57(6):1058-63.

Ngandu T, von Strauss E, Helkala EL, et al. Education and dementia: what lies behind the association? Neurology 2007;69(14):1442-50.

Nickelsen T, Lufkin EG, Riggs BL, et al. Raloxifene hydrochloride, a selective estrogen receptor modulator: safety assessment of effects on cognitive function and mood in postmenopausal women. Psychoneuroendocrinology 1999;24(1):115-28.

Niti M, Yap KB, Kua EH, et al. APOE-epsilon4, depressive symptoms, and cognitive decline in Chinese older adults: Singapore Longitudinal Aging Studies. J Gerontol A Biol Sci Med Sci 2009;64(2):306-11.

Niti M, Yap KB, Kua EH, et al. Physical, social and productive leisure activities, cognitive decline and interaction with APOE-epsilon 4 genotype in Chinese older adults. Int Psychogeriatr 2008;20(2):237-51.

Okereke OI, Kang JH, Cook NR, et al. Type 2 diabetes mellitus and cognitive decline in two large cohorts of community-dwelling older adults. J Am Geriatr Soc 2008;56(6):1028-36.

Packard C, Westendorp R, Stott D, et al. Association between apolipoprotein E4 and cognitive decline in elderly adults. J Am Geriatr Soc 2007;55(11):1777-85.

Panza F, D'Introno A, Colacicco AM, et al. Depressive symptoms, vascular risk factors and mild cognitive impairment. The Italian longitudinal study on aging. Dement Geriatr Cogn Disord 2008;25(4):336-46.

Paterniti S, Verdier-Taillefer MH, Dufouil C, et al. Depressive symptoms and cognitive decline in elderly people. Longitudinal study. Br J Psychiatry 2002;181:406-10.

Peila R, White LR, Masaki K, et al. Reducing the risk of dementia: efficacy of long-term treatment of hypertension. Stroke 2006;37(5):1165-70.

Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352(23):2379-88.

Plassman BL, Havlik RJ, Steffens DC, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 2000;55(8):1158-66.

Podewils LJ, Guallar E, Kuller LH, et al. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. Am J Epidemiol 2005;161(7):639-51.

Posner HB, Tang MX, Luchsinger J, et al. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology 2002;58(8):1175-81.

Potter GG, Plassman BL, Helms MJ, et al. Occupational characteristics and cognitive performance among elderly male twins. Neurology 2006;67(8):1377-82.

Price JF, Stewart MC, Deary IJ, et al. Low dose aspirin and cognitive function in middle aged to elderly adults: randomised controlled trial. BMJ 2008;337:a1198.

Prince M, Cullen M, Mann A. Risk factors for Alzheimer's disease and dementia: a case-control study based on the MRC elderly hypertension trial. Neurology 1994;44(1):97-104.

Prince M, Rabe-Hesketh S, Brennan P. Do antiarthritic drugs decrease the risk for cognitive decline? An analysis based on data from the MRC treatment trial of hypertension in older adults. Neurology 1998;50(2):374-9.

Prince MJ, Bird AS, Blizard RA, et al. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. BMJ 1996;312(7034):801-5.

Qiu C, Winblad B, Fastbom J, et al. Combined effects of APOE genotype, blood pressure, and antihypertensive drug use on incident AD. Neurology 2003;61(5):655-60.

Ravaglia G, Forti P, Lucicesare A, et al. Physical activity and dementia risk in the elderly: findings from a prospective Italian study. Neurology 2008;70(19 Pt 2):1786-94.

Ravaglia G, Forti P, Lucicesare A, et al. Prevalent depressive symptoms as a risk factor for conversion to mild cognitive impairment in an elderly Italian cohort. Am J Geriatr Psychiatry 2008;16(10):834-43.

Ravaglia G, Forti P, Maioli F, et al. Homocysteine and folate as risk factors for dementia and Alzheimer disease. Am J Clin Nutr 2005;82(3):636-43.

Ravaglia G, Forti P, Maioli F, et al. Risk factors for dementia: data from the Conselice

study of brain aging. Arch Gerontol Geriatr 2007;44 Suppl 1:311-20.

Rea T, Breitner J, Psaty B, et al. Statin use and the risk of incident dementia: the Cardiovascular Health Study. Arch Neurol 2005;62(7):1047-51.

Reitz C, den Heijer T, van Duijn C, et al. Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. Neurology 2007;69(10):998-1005.

Reitz C, Luchsinger J, Tang MX, et al. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. Neurology 2005;64(8):1378-83.

Reitz C, Tang MX, Manly J, et al. Hypertension and the risk of mild cognitive impairment. Arch Neurol 2007;64(12):1734-40.

Reitz C, Tang M-X, Luchsinger J, et al. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol 2004;61(5):705-14.

Rondeau V, Jacqmin-Gadda H, Commenges D, et al. Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol 2009;169(4):489-96.

Rovio S, Kareholt I, Helkala EL, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol 2005;4(11):705-11.

Rovio S, Kareholt I, Viitanen M, et al. Work-related physical activity and the risk of dementia and Alzheimer's disease. Int J Geriatr Psychiatry 2007;22(9):874-82.

Ryan J, Carriere I, Scali J, et al. Life-time estrogen exposure and cognitive functioning in later life. Psychoneuroendocrinology 2009;34(2):287-98.

Saczynski JS, Pfeifer LA, Masaki K, et al. The effect of social engagement on incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol 2006;163(5):433-40.

Saxby BK, Harrington F, Wesnes KA, et al. Candesartan and cognitive decline in older patients with hypertension: a substudy of the SCOPE trial. Neurology 2008;70(19 Pt 2):1858-66.

Scarmeas N, Levy G, Tang MX, et al. Influence of leisure activity on the incidence of Alzheimer's disease. Neurology 2001;57(12):2236-42.

Scarmeas N, Luchsinger JA, Schupf N, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA 2009;302(6):627-37.

Scarmeas N, Stern Y, Mayeux R, et al. Mediterranean diet and mild cognitive impairment. Arch Neurol 2009;66(2):216-25.

Scarmeas N, Stern Y, Tang MX, et al. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 2006;59(6):912-21.

Schaefer EJ, Bongard V, Beiser AS, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol 2006;63(11):1545-50.

Schuit AJ, Feskens EJ, Launer LJ, et al. Physical activity and cognitive decline, the role of the apolipoprotein e4 allele. Med Sci Sports Exerc 2001;33(5):772-7.

Seeman TE, Lusignolo TM, Albert M, et al. Social relationships, social support, and patterns of cognitive aging in healthy, high-functioning older adults: MacArthur studies of successful aging. Health Psychol 2001;20(4):243-55.

Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346(7):476-83.

Shadlen MF, Larson EB, Wang L, et al. Education modifies the effect of apolipoprotein epsilon 4 on cognitive decline. Neurobiol Aging 2005;26(1):17-24.

Shah RC, Wilson RS, Bienias JL, et al. Relation of blood pressure to risk of incident Alzheimer's disease and change in global cognitive function in older persons. Neuroepidemiology 2006;26(1):30-6.

Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004;291(24):2947-58.

Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289(20):2651-62.

Skoog I, Lithell H, Hansson L, et al. Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE). Am J Hypertens 2005;18(8):1052-9.

Slooter AJC, Cruts M, Hofman A, et al. The impact of APOE on myocardial infarction, stroke, and dementia: the Rotterdam Study. Neurology 2004;62(7):1196-8.

Smith A, Clark R, Nutt D, et al. Anti-Oxidant Vitamins and Mental Performance of the Elderly. Human Psychopharmacology Clinical and Experimental 1999;14:459-471.

Solfrizzi V, D'Introno A, Colacicco AM, et al. Alcohol consumption, mild cognitive impairment, and progression to dementia. Neurology 2007;68(21):1790-9.

Solfrizzi V, Panza F, Colacicco AM, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology 2004;63(10):1882-91.

Staehelin HB, Perrig-Chiello P, Mitrache C, et al. Apolipoprotein E genotypes and cognitive functions in healthy elderly persons. Acta Neurol Scand 1999;100(1):53-60.

Stott DJ, Falconer A, Kerr GD, et al. Does low to moderate alcohol intake protect against cognitive decline in older people? J Am Geriatr Soc 2008;56(12):2217-24.

Sturman MT, de Leon CF, Bienias JL, et al. Body mass index and cognitive decline in a biracial community population. Neurology 2008;70(5):360-7.

Swan GE, DeCarli C, Miller BL, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. Neurology 1998;51(4):986-93.

Szekely CA, Breitner JC, Fitzpatrick AL, et al. NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type. Neurology 2008;70(1):17-24.

Szwast SJ, Hendrie H, Lane K, et al. Association of statin use with cognitive decline in elderly African Americans. Neurology 2007;69(19):1873-80.

Tang MX, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. Neurology 2001;56(1):49-56.

Tervo S, Kivipelto M, Hanninen T, et al. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dement Geriatr Cogn Disord 2004;17(3):196-203.

Thal LJ, Ferris SH, Kirby L, et al. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology 2005;30(6):1204-15.

Tierney MC, Oh P, Moineddin R, et al. A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. Psychoneuroendocrinology 2009;34(7):1065-74.

Tyas SL, Salazar JC, Snowdon DA, et al. Transitions to mild cognitive impairments, dementia, and death: findings from the Nun Study. Am J Epidemiol 2007;165(11):1231-8.

Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003;163(9):1069-75.

Tzourio C, Dufouil C, Ducimetiere P, et al. Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. Epidemiology of Vascular Aging. Neurology 1999;53(9):1948-52.

Unverzagt FW, Kasten L, Johnson KE, et al. Effect of memory impairment on training outcomes in ACTIVE. J Int Neuropsychol Soc 2007;13(6):953-60.

van Gelder BM, Tijhuis M, Kalmijn S, et al. Marital status and living situation during a 5-year period are associated with a subsequent 10-year cognitive decline in older men: the FINE Study. J Gerontol B Psychol Sci Soc Sci 2006;61(4):P213-9.

Verghese J, LeValley A, Derby C, et al. Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. Neurology 2006;66(6):821-7.

Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. N Engl J Med 2003;348(25):2508-16.

Virtanen M, Singh-Manoux A, Ferrie JE, et al. Long working hours and cognitive function: the Whitehall II Study. Am J Epidemiol 2009;169(5):596-605.

Waldstein SR, Giggey PP, Thayer JF, et al. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. Hypertension 2005;45(3):374-9.

Wang HX, Wahlin A, Basun H, et al. Vitamin B(12) and folate in relation to the development of Alzheimer's disease. Neurology 2001;56(9):1188-94.

Wengreen HJ, Munger RG, Corcoran CD, et al. Antioxidant intake and cognitive function of elderly men and women: the Cache County Study. J Nutr Health Aging 2007;11(3):230-7.

Wetherell JL, Reynolds CA, Gatz M, et al. Anxiety, cognitive performance, and cognitive decline in normal aging. J Gerontol B Psychol Sci Soc Sci 2002;57(3):P246-55.

Williamson JD, Espeland M, Kritchevsky SB, et al. Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2009;64(6):688-94.

Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA 2006;296(23):2805-14.

Wilson RS, Bennett DA, Bienias JL, et al. Cognitive activity and cognitive decline in a biracial community population. Neurology 2003;61(6):812-6.

Wilson RS, Bienias JL, Berry-Kravis E, et al. The apolipoprotein E epsilon 2 allele and

decline in episodic memory. J Neurol Neurosurg Psychiatry 2002;73(6):672-7.

Wilson RS, Hebert LE, Scherr PA, et al. Educational attainment and cognitive decline in old age. Neurology 2009;72(5):460-5.

Wilson RS, Krueger KR, Arnold SE, et al. Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry 2007;64(2):234-40.

Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 2002;287(6):742-8.

Wilson RS, Scherr PA, Hoganson G, et al. Early life socioeconomic status and late life risk of Alzheimer's disease. Neuroepidemiology 2005;25(1):8-14.

Wilson RS, Scherr PA, Schneider JA, et al. Relation of cognitive activity to risk of developing Alzheimer disease. Neurology 2007;69(20):1911-20.

Wilson RS, Schneider JA, Boyle PA, et al. Chronic distress and incidence of mild cognitive impairment. Neurology 2007;68(24):2085-92.

Winnock M, Letenneur L, Jacqmin-Gadda H, et al. Longitudinal analysis of the effect of apolipoprotein E epsilon4 and education on cognitive performance in elderly subjects: the PAQUID study. J Neurol Neurosurg Psychiatry 2002;72(6):794-7.

Wright CB, Elkind MS, Luo X, et al. Reported alcohol consumption and cognitive decline: The northern Manhattan study. Neuroepidemiology 2006;27(4):201-7.

Xu WL, von Strauss E, Qiu CX, et al. Uncontrolled diabetes increases the risk of Alzheimer's disease: a population-based cohort study. Diabetologia 2009;52(6):1031-9.

Yaffe K, Barnes D, Nevitt M, et al. A prospective study of physical activity and cognitive decline in elderly women: women who walk. Arch Intern Med 2001;161(14):1703-8.

Yaffe K, Blackwell T, Gore R, et al. Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. Arch Gen Psychiatry 1999;56(5):425-30.

Yaffe K, Cauley J, Sands L, et al. Apolipoprotein E phenotype and cognitive decline in a prospective study of elderly community women. Arch Neurol 1997;54(9):1110-4.

Yaffe K, Fiocco AJ, Lindquist K, et al. Predictors of maintaining cognitive function in older adults: the Health ABC study. Neurology 2009;72(23):2029-35.

Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 2004;292(18):2237-42.

Yasar S, Corrada M, Brookmeyer R, et al. Calcium channel blockers and risk of AD: the Baltimore Longitudinal Study of Aging. Neurobiol Aging 2005;26(2):157-63.

Yesavage JA, Friedman L, Ashford JW, et al. Acetylcholinesterase inhibitor in combination with cognitive training in older adults. J Gerontol B Psychol Sci Soc Sci 2008;63(5):P288-94.

Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. Neurology 1995;45(6):1161-8.

Yu F, Ryan LH, Schaie KW, et al. Factors associated with cognition in adults: the Seattle Longitudinal Study. Res Nurs Health 2009;32(5):540-50.

Zandi P, Sparks D, Khachaturian A, et al. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. Arch Gen Psychiatry 2005;62(2):217-24.

Zandi PP, Anthony JC, Hayden KM, et al. Reduced incidence of AD with NSAID but not H2 receptor antagonists: the Cache County Study. Neurology 2002;59(6):880-6.

Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 2004;61(1):82-8.

Zunzunegui MV, Alvarado BE, Del Ser T, et al. Social networks, social integration, and social engagement determine cognitive decline in community-dwelling Spanish older adults. J Gerontol B Psychol Sci Soc Sci 2003;58(2):S93-S100.

Appendix C. Quality Assessment – Systematic Reviews*

For reviews, first determine whether it is a systematic review (SR). To be a systematic review, it must include a methods section that describes (1) a search strategy and (2) an a priori approach to synthesizing the data. For reviews determined to meet the SR criteria, assess methodological quality.

General instructions:

Step 1: Grade each of the criteria listed below as "Yes," "No," "Partially," or "Can't tell." Factors to consider when making an assessment are listed under each criterion. Where appropriate (particularly when assigning a "No," "Partially," or "Can't tell" score), please provide a brief rationale for your decision (in parentheses).

1. **Is a focused clinical question clearly stated?**
    a. At a minimum, question should clearly identify population and outcomes
    b. Does not have to be in PICO format (Population, Intervention, Comparisons, Outcomes)

2. **Are the search methods used to identify relevant studies clearly described?**
    a. Search methods described in enough detail to permit replication

3. **Was the search for evidence reasonably comprehensive?**
    a. Search included MEDLINE and other appropriate databases

4. **Are the inclusion/exclusion criteria used to screen primary studies clearly described?**
    a. Inclusion/exclusion criteria described in enough detail to permit replication

5. **Were the inclusion/exclusion criteria appropriate (aimed at avoiding bias in the included studies)?**
    a. Criteria likely to capture all relevant studies (consider especially criteria related to study population, risk factor/intervention, outcomes, and study design)

6. **Were the primary studies assessed for quality using clearly stated criteria?**
    a. Quality assessment was done, and criteria used to assess study quality were specified in enough detail to permit replication

* Adapted from Marinopoulos et al., 2007[1] and Moher et al., 1999.[2]

7. **Was the quality assessment done appropriately?**
    a. Quality assessment was performed using a validated instrument (with citation), or the authors demonstrated the validity of their methods.

8. **Were the methods used to assess primary studies reproducible?**
    a. Did two or more raters make inclusion/exclusion decisions, abstract data, and assess study quality – either independently or with one over-reading?
    b. Was an appropriate method used to resolve disagreements?

9. **Did the authors discuss whether any variation observed in the results of the primary studies might be due to differences in study design or population?**
    a. Text or tables provide comparative information on most of following: study design, populations, interventions, and outcome measures
    b. Authors discuss possible sources of heterogeneity

10. **Were the results of the relevant studies combined appropriately?**
    a. Some assessment of qualitative or quantitative assessment heterogeneity of study results
    b. Accepted qualitative or quantitative method of pooling used (i.e., more than simple addition; e.g., random-effects vs. fixed-effect model for quantitative data)

11. **Was publication bias assessed?**
    a. Publication bias tested for using funnel plots, test statistics, or search of trials registry for unpublished studies.

12. **Are the stated conclusions supported by the data presented?**

Step 2: Rate the overall quality of the SR as "Good," "Fair," or "Poor" using the guidance below.

Good = After considering items 1-11, item 12 is rated "Yes" with no important limitations. This means that few of the items 1-11 are rated "Partially" or "No," and none of the limitations are thought to decrease the validity of the conclusions.

Fair = After considering items 1-11, item 12 is rated "Yes," but with at least some important limitations. This means that enough of the items 1-11 are rated "Partially" or "No" to introduce some uncertainty about the validity of the conclusions.

Poor = After considering items 1-11, item 12 is rated "No." This means that several of items 1-11 are rated "Partially" or "No," introducing serious uncertainty about the validity of the conclusions.

References

1. Marinopoulos S, Dorman T, Ratanawongsa N, et al. Effectiveness of Continuing Medical Education. Evidence Report/Technology Assessment No. 149 (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 07-E006. Rockville, MD:Agency for Healthcare Research and Quality. January 2007. Available at http://www.ahrq.gov/clinic/tp/cmetp.htm. Accessed on September 29, 2009.

2. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354(9193):1896-900.

Appendix D. Quality Assessment – RCTs

Quality Assessment – RCTs*

General instructions: Grade each criterion as "Yes," "No," "Partially," or "Can't tell." Factors to consider when making an assessment are listed under each criterion. Where appropriate (particularly when assigning a "No," "Partially," or "Can't tell" score), please provide a brief rationale for your decision (in parentheses) in the evidence table.

1. **Were the groups similar at baseline in terms of baseline characteristics and prognostic factors?** (Consider baseline prognostic characteristics of intervention/control groups including age, sex, race, educational level, general medical conditions, and performance on a cognitive measure.)
    a. No important baseline differences
    b. Important baseline differences
    c. Can't tell if important baseline differences (not reported or key baseline characteristics not reported)

2. **Were AD/cognitive outcomes assessed using a valid methodology and criteria?** *(See details below.)*
    a. Valid method used (assessment method and definition)
    b. Valid method used only in some of the subjects
    c. Valid method not used

3. **Were subjects and providers blind to the intervention/exposure status of participants?**
    a. Subjects blind to exposure/intervention
    b. Providers blind to exposure/intervention

4. **Were outcome assessors blind to exposure/intervention status?**

5. **Were incomplete outcome data adequately addressed?** *(See more detailed guidance below.)*

6. **Was the differential loss to follow-up between the compared groups low (defined as < 10%)?***
    a. *Note: If event rates (e.g., conversion to AD) are low, then even smaller differences in f/u by group could lead to large biases in estimate of effect.

7. **Was the overall loss to follow-up low (defined as < 30%)?**

* Taken from AHRQ et al., 2007[1] and Higgins et al., 2008.[2]

a. Where different numbers of patients are followed up for different outcomes, use the number followed up for the primary outcome for this calculation.

8. Conflict of interest reported and insignificant?
   a. Is the source of funding identified?
   b. Is the funding from a source that does *not* have a vested interest in the study results?

9. Were the methods used for randomization adequate?
   a. Yes, true random number generator (e.g., computer randomization)
   b. No, not true random number generator (e.g., every other, odd or even DOB, patient record number)

10. Was allocation concealment adequate? (Allocation sequence should be described in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment.)
   a. Allocation concealment was adequate (e.g., call central number for intervention allocation after eligibility confirmed, sequentially numbered sealed opaque envelopes, sequentially numbered drug containers of identical appearance)
   b. Allocation concealment inadequate

****

Detailed guidance for Item 2 – assessment of AD/cognitive outcomes

Principles for an acceptable criterion standard for diagnosis of AD:

1. Uses established diagnostic criteria (e.g., DSM-IV, NINCDS-ADRDA, ICD or similar).
2. Uses an acceptable method for obtaining the necessary data to apply the diagnostic criteria, defined as an in-person assessment using an assessment battery that addresses the key domains in the diagnostic criteria, namely, at least memory plus one or more of the following: orientation, agnosia, aphasia, apraxia, executive function, or effect on functional status. If the diagnosis is from medical records only, need evidence that a formal in-person evaluation was done to determine the diagnosis of AD.
3. Pathological specimens alone are not satisfactory since AD is a clinical diagnosis. If AD is diagnosed using an acceptable criterion standard, then pathological specimens could provide useful supplementary information.

Principles for an acceptable criterion standard for diagnosis of cognitive decline:

1. An agreed upon set of diagnostic criteria for a categorical diagnosis (e.g., MCI, CIND, or similar as described in text). The diagnostic criteria will vary across studies, but each study should provide details of the criteria used for MCI, CIND, or similar diagnostic terms for mild cognitive symptoms. The definition should

include mild cognitive impairment reported by the individual or informant that did not meet criteria for dementia, or performance on neuropsychological measures that was both below expectation and considered to be in the impaired range based on normative standards.

2. An acceptable method for obtaining the necessary data to apply the diagnostic criteria, defined as an in-person assessment using an assessment battery that addresses the key domains in the diagnostic criteria, namely, at least memory plus one or more of the following: orientation, agnosia, aphasia, apraxia, executive function, and evidence that cognitive impairment does *not* significantly interfere with functional status. If the diagnosis is from medical records only, need evidence that a formal in-person evaluation was done to determine the diagnosis of mild impairment.
3. If cognition is assessed at two or more time points, then change on a validated instrument.

****

Detailed guidance for Item 5 ("Were incomplete outcome data adequately addressed?") – taken from *Cochrane Handbook for Systematic Reviews of Interventions*[2], Table 8.5.c

Criteria for a judgment of "Yes" (i.e., low risk of bias)	**Any *one* of the following:** - No missing outcome data; - Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); - Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; *(see example below) - For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; - Missing data have been imputed using appropriate methods.
Criteria for the judgment of "No" (i.e., high risk of bias)	**Any *one* of the following:** - Reason for missing outcome data likely to be related to true outcome, with either imbalance in

	numbers or reasons for missing data across intervention groups; - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; ; *(see example below) - For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; - "As-treated" analysis done with substantial departure of the intervention received from that assigned at randomization; - Potentially inappropriate application of simple imputation.
Criteria for the judgment of "Can't tell" (uncertain risk of bias)	**Any *one* of the following:** - Insufficient reporting of attrition/exclusions to permit judgment of "Yes" or "No" (e.g., number randomized not stated, no reasons for missing data provided); - Study did not address/report this outcome.

***Example for risk of bias due to incomplete follow-up**
Historically, methodologists have sometimes suggested somewhat arbitrary thresholds for acceptable loss to follow-up (e.g. less than 20%). The significance of particular rates of loss to follow-up, however, varies widely and is dependent on the relation between loss to follow-up and number of events. For instance, loss to follow-up of 5% in both intervention and control groups provides little threat to bias if event rates were 20% and 40% in intervention and control groups respectively. If event rates were 2% and 4%, however, concern with 5% loss to follow-up is much greater.

Example where lost to f/u is a relatively low proportion of those with events and little risk of bias. RR=0.5 (.21/.42) and if assumed all lost to f/u had events, RR=0.55 (0.25/0.45)

	Enrolled/FU outcomes	Lost to F/U	Event rate	Event rate if lost to f/u had events
Intervention	100/95	5	20/95=.21	25/100=.25
Control	100/95	5	40/95=.42	45/100=.45

Example where lost to f/u is a relatively higher proportion of those with events and significant risk of bias. It only takes a few lost to follow to have had events to change the difference in event rates substantially. RR=0.5 (.02/.04) and if assumed all lost to f/u

had events, RR=0.78 (0.07/0.09) and may be distorted further if event rates in the lost to f/u differed between intervention and control

	Enrolled/FU outcomes	Lost to F/U	Event rate	Event rate if lost to f/u had events
Intervention	100/95	5	2/95=.02	7/100=.07
Control	100/95	5	4/95=.04	9/100=.09

References

1. Agency for Healthcare Research and Quality. Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 [Draft posted Oct. 2007]. Rockville, MD:Agency for Healthcare Research and Quality. Available at: http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf. Accessed September 3, 2009.

2. Higgins J, Altman D. Assessing the risk of bias. In: Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions (version 5.0.1) updated September 2008.*: The Cochrane Collaboration.

Appendix E. Quality Assessment – Observational Studies

General instructions: Grade each criterion as "Yes," "No," "Partially," or "Can't tell." Factors to consider when making an assessment are listed under each criterion. Where appropriate (particularly when assigning a "No," "Partially," or "Can't tell" score), please provide a brief rationale for your decision (in parentheses) in the evidence table. Criteria marked *italics* are considered the most essential quality indicators for our purposes.

1) Unbiased selection of the cohort?

Factors that help *reduce* selection bias:

- Prospective study design and recruitment of subjects
- Inclusion/exclusion criteria
    - Clearly described (especially re: age and cognitive status)
    - Assessed using valid and reliable measures
- Recruitment strategy
    - Clearly described
    - Relatively free from bias (selection bias might be introduced, e.g., by recruitment via advertisement)

2) Selection minimizes baseline differences in prognostic factors?

Factors to consider:

- Was selection of the comparison group appropriate?
  Note: This may not be an issue in the cohort studies we review. In general, the exposed and unexposed groups should be from the same source. However, it is possible that for some medical condition exposures the exposed group will be patients from a specialty medical clinic and the unexposed comparison group will be from another source. Consider whether these two sources are likely to differ on factors related to the outcome (besides the exposure factor).
- In addition to selecting the cohort in an unbiased way, did study investigators do other things to ensure that exposed/unexposed groups were comparable, e.g., by using stratification, matching, or propensity scores?

3) Sample size calculated/5% difference?

Factors to consider:

- Did the authors report conducting a power analysis or describe some other basis for determining the adequacy of study group sizes for the primary outcome(s) of interest to us?
- Was the sample size sufficiently large to detect a clinically significant difference of 5% in event rates or an OR/RR increase of ≥ 1.5 or decrease of ≥ 0.67 between groups in at least one primary outcome measure of interest to us?

4) Adequate description of the cohort?

Consider whether the cohort is well-characterized in terms of baseline:

- Age
- Sex

- Race
- Educational level
- Cognitive status
- *For genetic association studies,* were the diseased and non-diseased populations drawn from groups with the same ethnic/racial mix?

5) Validated method for ascertaining exposure?

Factors to consider:

- Was the method used to ascertain exposure clearly described? (Details should be sufficient to permit replication in new studies.)
- Was a valid and reliable measure used to ascertain exposure? (Subjective measures based on self-report tend to have lower reliability and validity than objective measures such as clinical reports and lab findings.)
- *For gene association studies,* is the "call rate" of genotyping (the proportion of samples in which the genotyping provides an unambiguous reading) reported? Were quality checks implemented or rules established to determine when genotyping results would be considered valid?

To clarify your score, please make a note of the method/measure used to ascertain exposure.

6) Validated method for ascertaining clinical outcomes?

Factors to consider:

- Were primary outcomes (AD and/or cognitive decline) assessed using valid and reliable measures? *(See details below.)*
- Were these measures implemented consistently across all study participants?

7) Outcome assessment blind to exposure?

- Were the study investigators who assessed outcomes blind to the intervention or exposure status of participants?

8) Adequate follow-up period?

Factors to consider:

- Minimum adequate follow-up period is 2 years for AD and 1 year for cognitive decline
- Follow-up period should be the same for all groups
    - In cohort studies, length of follow-up should be the same across all groups.
    - In nested case-control studies, period between the intervention/exposure and outcome should be the same for cases and controls.
    - OK if differences in follow-up time were adjusted for using statistical techniques, e.g., survival analysis.

9) Completeness of follow-up?

Factors to consider:

- Did attrition from any group exceed 30%? (Attrition is measured in relation to the time between baseline/allocation and outcome measurement. Where different numbers of patients are followed up for different outcomes, use the number followed up for the primary outcome for this calculation.)
- Did attrition differ between groups by more than 10% percent?

10) Analysis controls for confounding?

Factors to consider:

- Did the analysis control for any baseline differences between groups?
- Does the study identify and control for important confounding variables and effect modifiers? (Confounding variables are risk factors that are correlated with the intervention/exposure and outcome and may therefore bias the estimation of the effect of intervention/exposure on outcome if unmeasured. Effect modifiers are not correlated with the intervention/exposure, but change the effect of the intervention/exposure on the outcome. Age, race/ethnicity, education, and measures of SES are examples of effect modifiers and confounding variables for the exposures and outcomes of interest in this study.)

11) Analytic methods appropriate?

Factors to consider:

- Was the kind of analysis done appropriate for the kind of outcome data?
    - Dichotomous – logistic regression, survival
    - Categorical – mixed model for categorical outcomes
    - Continuous – ANCOVA, mixed model
- Was the analysis done on an intention-to-treat basis? (That is, was the impact of loss to follow-up [or differential loss to followup] assessed, e.g., through sensitivity analysis or another intent-to-treat adjustment method?
- Was the number of variables used in the analysis appropriate for the sample size? (The statistical techniques used must be appropriate to the data and take into account issues such as controlling for small sample size, clustering, rare outcomes, multiple comparison, and number of covariates for a given sample size. The multiple comparisons issue may be a problem particularly when performance results on numerous cognitive measures are being compared. When assessing change on cognitive measure over time, consider whether change score should be adjusted for baseline score, and consider distribution of baseline scores and change scores.)
- *For gene association studies:*
    - Did the investigators conduct statistical tests to check whether the observed genotype frequencies are consistent with the Hardy-Weinberg Equilibrium?
    - Did the investigators adjust for multiple comparisons?

****

Detailed guidance for Item 6 – assessment of AD/cognitive outcomes

Principles for an acceptable criterion standard for diagnosis of AD:

1. Uses established diagnostic criteria (e.g., DSM-IV, NINCDS-ADRDA, ICD or similar).
2. Uses an acceptable method for obtaining the necessary data to apply the diagnostic criteria, defined as an in-person assessment using an assessment battery that addresses the key domains in the diagnostic criteria, namely, at least memory plus one or more of the following: orientation, agnosia, aphasia, apraxia, executive function, or effect on functional status. If the diagnosis is from medical records only, need evidence that a formal in-person evaluation was done to determine the diagnosis of AD.
3. Pathological specimens alone are not satisfactory since AD is a clinical diagnosis. If AD is diagnosed using an acceptable criterion standard, then pathological specimens could provide useful supplementary information.

Principles for an acceptable criterion standard for diagnosis of cognitive decline:

1. An agreed upon set of diagnostic criteria for a categorical diagnosis (e.g., MCI, CIND, or similar as described in text). The diagnostic criteria will vary across studies, but each study should provide details of the criteria used for MCI, CIND, or similar diagnostic terms for mild cognitive symptoms. The definition should include mild cognitive impairment reported by the individual or informant that did not meet criteria for dementia, or performance on neuropsychological measures that was both below expectation and considered to be in the impaired range based on normative standards.
2. An acceptable method for obtaining the necessary data to apply the diagnostic criteria, defined as an in-person assessment using an assessment battery that addresses the key domains in the diagnostic criteria, namely, at least memory plus one or more of the following: orientation, agnosia, aphasia, apraxia, executive function, and evidence that cognitive impairment does *not* significantly interfere with functional status. If the diagnosis is from medical records only, need evidence that a formal in-person evaluation was done to determine the diagnosis of mild impairment.
3. If cognition is assessed at two or more time points, then change on a validated instrument.

Appendix F. Peer Reviewers

The Duke Evidence-based Practice Center is grateful to the following peer reviewers who read and commented on a draft version of this report:

Jesse Berlin, ScD; Pharmaceutical Research & Development; Johnson & Johnson Pharmaceuticals; Titusville, NJ

Soo Borson, MD; Department of Psychiatry; University of Washington; Seattle, WA

Ornit Chiba-Falek, PhD; Institute for Genome Sciences and Policy; Duke University; Durham, NC

Mary Ganguli, MD, MPH; Department of Psychiatry; University of Pittsburgh; Pittsburgh, PA

Tiffany Hughes, PhD, MPH; Department of Psychiatry; University of Pittsburgh; Pittsburgh, PA

Dan Kaufer, MD; Department of Neurology; University of North Carolina; Chapel Hill, NC

Eric B. Larson, MD, MPH, MACP; Group Health Research Institute; Seattle WA

Appendix G. Excluded Studies

All excluded studies listed below (in alphabetical order) were reviewed in their full-text version. Following each reference, in italics, is the reason for exclusion. "Excluded," in this context, means "not included for data abstraction." Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Aartsen MJ, Smits CHM, van Tilburg T, et al. Activity in older adults: cause or consequence of cognitive functioning? A longitudinal study on everyday activities and cognitive performance in older adults. Journals of Gerontology Series B-Psychological Sciences & Social Sciences 2002;57(2):P153-62.
Full Text: Exclude - not longitudinal

Aevarsson O, Skoog I. A longitudinal population study of the mini-mental state examination in the very old: relation to dementia and education. Dement Geriatr Cogn Disord 2000;11(3):166-75.
Full Text: Exclude - not applicable population

Agostini JV, Tinetti ME, Han L, et al. Effects of statin use on muscle strength, cognition, and depressive symptoms in older adults. J Am Geriatr Soc 2007;55(3):420-5.
Full Text: Exclude - dementia @ baseline

Akbaraly NT, Faure H, Gourlet V, et al. Plasma carotenoid levels and cognitive performance in an elderly population: results of the EVA Study. J Gerontol A Biol Sci Med Sci 2007;62(3):308-16.
Full Text: Exclude - not longitudinal

Akbaraly TN, Singh-Manoux A, Marmot MG, et al. Education attenuates the association between dietary patterns and cognition. Dement Geriatr Cogn Disord 2009;27(2):147-54.
Full Text: Exclude - not longitudinal

Akiyama H, Meyer JS, Mortel KF, et al. Normal human aging: factors contributing to cerebral atrophy. J Neurol Sci 1997;152(1):39-49.
Full Text: Exclude - outcome non-specific AD

Albert MS, Jones K, Savage CR, et al. Predictors of cognitive change in older persons: MacArthur studies of successful aging. Psychol Aging 1995;10(4):578-89.
Full Text: Exclude - unable to extract results

Aleman A, Muller M, de Haan EH, et al. Vascular risk factors and cognitive function in a sample of independently living men. Neurobiol Aging 2005;26(4):485-90.
Full Text: Exclude - not longitudinal

Alexander CN, Langer EJ, Newman RI, et al. Transcendental meditation, mindfulness, and longevity: an experimental study with the elderly. J Pers Soc Psychol 1989;57(6):950-64.
Full Text: Exclude - dementia @ baseline

Almeida OP, Norman P, Hankey G, et al. Successful mental health aging: results from a longitudinal study of older Australian men. Am J Geriatr Psychiatry 2006;14(1):27-35.
Full Text: Exclude - not longitudinal

Ampuero I, Ros R, Royuela A, et al. Risk factors for dementia of Alzheimer type and aging-associated cognitive decline in a Spanish population based sample, and in brains with pathology confirmed Alzheimer's disease. J Alzheimers Dis 2008;14(2):179-91.
Full Text: Exclude - dementia @ baseline

Ancelin ML, Artero S, Portet F, et al. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ 2006;332(7539):455-9.
Full Text: Exclude - risk factor out of scope

Andel R, Crowe M, Pedersen NL, et al. Complexity of work and risk of Alzheimer's disease: a population-based study of Swedish twins. Journals of Gerontology Series B-Psychological Sciences & Social Sciences 2005;60(5):P251-8.
Full Text: Exclude - not longitudinal

Andersen G, Vestergaard K, Riis JO, et al. Dementia of depression or depression of dementia in stroke? Acta Psychiatr Scand 1996;94(4):272-8.
Full Text: Exclude - risk factor out of scope

Andersen K, Launer LJ, Ott A, et al. Do nonsteroidal anti-inflammatory drugs decrease the risk for Alzheimer's disease? The Rotterdam Study. Neurology 1995;45(8):1441-5.
Full Text: Exclude - not longitudinal

Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial.[see comment]. JAMA 2004;291(14):1701-12.
Full Text: Exclude - no cognitive endpoints

Andre-Petersson L, Elmstahl S, Hagberg B, et al. Is blood pressure at 68 an independent predictor of cognitive decline at 81? Results from follow-up study "Men born in 1914", Malmo, Sweden. Aging Ment Health 2003;7(1):61-72.
Full Text: Exclude - observational N < 300

Andrieu S, Gillette S, Amouyal K, et al. Association of Alzheimer's disease onset with ginkgo biloba and other symptomatic cognitive treatments in a population of women aged 75 years and older from the EPIDOS study. J Gerontol A Biol Sci Med Sci 2003;58(4):372-7.
Full Text: Exclude - outcomes inadequately assessed

Andrieu S, Ousset PJ, Coley N, et al. GuidAge study: a 5-year double blind, randomised trial of EGb 761 for the prevention of Alzheimer's disease in elderly subjects with memory complaints. i. rationale, design and baseline data. Curr Alzheimer Res 2008;5(4):406-15.
Full Text: Exclude - insufficient outcomes data

Annerbo S, Wahlund LO, Lokk J. The significance of thyroid-stimulating hormone and homocysteine in the development of Alzheimer's disease in mild cognitive impairment: a 6-year follow-up study. Am J Alzheimers Dis Other Demen 2006;21(3):182-8.
Full Text: Exclude - observational N<300

Anonymous. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129(4):687-702.
Full Text: Exclude - Methods paper

Anonymous. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group.[see comment]. N Engl J Med 1989;321(3):129-35.
Full Text: Exclude - outcomes not AD/CD

Anonymous. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group.[see comment]. JAMA 1991;265(24):3255-64.
Full Text: Exclude - outcomes unacceptably assessed

Anonymous. The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. Neurology 1994;44(11):2073-80.
Full Text: Exclude - not longitudinal

Anonymous. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials 1998;19(1):61-109.
Full Text: Exclude - methods paper

Anonymous. Potassium may help prevent Alzheimer's disease. Potassium could be a possible deterrent for dementia, three new studies suggest. Health News 2006;12(6):7-8.
Full Text: Exclude - dementia @ baseline

Anthony JC, Breitner JC, Zandi PP, et al. Reduced prevalence of AD in users of NSAIDs and H2 receptor antagonists: the Cache County study. Neurology 2000;54(11):2066-71.
Full Text: Exclude - not longitudinal

Arauz A, Alonso E, Rodriguez-Saldana J, et al. Cognitive impairment and mortality in older healthy Mexican subjects: a population-based 10-year follow-up study. Neurol Res 2005;27(8):882-6.
Full Text: Exclude - non-Western country

Arlt S, Schulze F, Eichenlaub M, et al. Asymmetrical dimethylarginine is increased in plasma and decreased in cerebrospinal fluid of patients with Alzheimer's disease. Dement Geriatr Cogn Disord 2008;26(1):58-64.
Full Text: Exclude - not longitudinal

Aronson MK, Ooi WL, Morgenstern H, et al. Women, myocardial infarction, and dementia in the very old. Neurology 1990;40(7):1102-6.
Full Text: Exclude - risk factor out of scope

Arvanitakis Z, Schneider JA, Wilson RS, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Neurology 2006;67(11):1960-5.
Full Text: Exclude - outcomes not AD/CD

Arvanitakis Z, Wilson RS, Li Y, et al. Diabetes and function in different cognitive systems in older individuals without dementia. Diabetes Care 2006;29(3):560-5.
Full Text: Exclude - not longitudinal

Arve S, Tilvis RS, Lehtonen A, et al. Coexistence of lowered mood and cognitive impairment of elderly people in five birth cohorts. Aging (Milano) 1999;11(2):90-5.
Full Text: Exclude - not longitudinal

Ashman TA, Cantor JB, Gordon WA, et al. A comparison of cognitive functioning in older adults with and without traumatic brain injury. J Head Trauma Rehabil 2008;23(3):139-48.
Full Text: Exclude - not longitudinal

Atiea JA, Moses JL, Sinclair AJ. Neuropsychological function in older subjects with non-insulin-dependent diabetes mellitus. Diabet Med 1995;12(8):679-85.
Full Text: Exclude - not longitudinal

Atkinson HH, Cesari M, Kritchevsky SB, et al. Predictors of combined cognitive and physical decline. J Am Geriatr Soc 2005;53(7):1197-202.
Full Text: Exclude - not applicable population

Bachman DL, Wolf PA, Linn RT, et al. Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. Neurology 1993;43(3 Pt 1):515-9.
Full Text: Exclude - risk factor out of scope

Baldeiras I, Santana I, Proenca MT, et al. Peripheral oxidative damage in mild cognitive impairment and mild Alzheimer's disease. J Alzheimers Dis 2008;15(1):117-28.
Full Text: Exclude - not longitudinal

Ban TA, Morey L, Aguglia E, et al. Nimodipine in the treatment of old age dementias. Prog Neuropsychopharmacol Biol Psychiatry 1990;14(4):525-

51.
Full Text: Exclude - not longitudinal

Barnes DE, Covinsky KE, Whitmer RA, et al. Predicting risk of dementia in older adults. The late-life dementia risk index. Neurology 2009.
Full Text: Exclude - <60% of dementia is AD

Barnes DE, Tager IB, Satariano WA, et al. The relationship between literacy and cognition in well-educated elders. J Gerontol A Biol Sci Med Sci 2004;59(4):390-5.
Full Text: Exclude - not longitudinal

Barrett-Connor E, Edelstein SL. A prospective study of dehydroepiandrosterone sulfate and cognitive function in an older population: the Rancho Bernardo Study. J Am Geriatr Soc 1994;42(4):420-3.
Full Text: Exclude - not longitudinal

Basaria S, Wisniewski A, Dupree K, et al. Effect of high-dose isoflavones on cognition, quality of life, androgens, and lipoprotein in post-menopausal women. J Endocrinol Invest 2009;32(2):150-5.
Full Text: Exclude - CD f/u < 1 yr

Bassuk SS, Berkman LF, Wypij D. Depressive symptomatology and incident cognitive decline in an elderly community sample. Arch Gen Psychiatry 1998;55(12):1073-81.
Full Text: Exclude - SPMSQ single test

Bassuk SS, Glass TA, Berkman LF. Social disengagement and incident cognitive decline in community-dwelling elderly persons. Ann Intern Med 1999;131(3):165-73.
Full Text: Exclude - SPMSQ single test

Bathum L, von Bornemann Hjelmborg J, Christiansen L, et al. Methylenetetrahydrofolate reductase 677C>T and methionine synthase 2756A>G mutations: no impact on survival, cognitive functioning, or cognitive decline in nonagenarians. J Gerontol A Biol Sci Med Sci 2007;62(2):196-201.
Full Text: Exclude - dementia @ baseline BPIncl

Battino M, Bompadre S, Leone L, et al. Coenzyme Q, Vitamin E and Apo-E alleles in Alzheimer Disease. Biofactors 2003;18(1-4):277-81.
Full Text: Exclude - dementia @ baseline

Beard CM, Waring SC, O'Brien PC, et al. Nonsteroidal anti-inflammatory drug use and Alzheimer's disease: a case-control study in Rochester, Minnesota, 1980 through 1984. Mayo Clin Proc 1998;73(10):951-5.
Full Text: Exclude - outcome non-specific AD

Becker JT, Chang YF, Lopez OL, et al. Depressed mood is not a risk factor for incident dementia in a community-based cohort. Am J Geriatr Psychiatry 2009;17(8):653-63.
Full Text: Exclude - observational N<300

Beeri MS, Schmeidler J, Silverman JM, et al. Insulin in combination with other diabetes medication is associated with less Alzheimer neuropathology. Neurology 2008;71(10):750-7.
Full Text: Exclude - selected population

Beeri MS, Silverman JM, Davis KL, et al. Type 2 diabetes is negatively associated with Alzheimer's disease neuropathology. J Gerontol A Biol Sci Med Sci 2005;60(4):471-5.
Full Text: Exclude - not applicablel population

Bennett DA, Whitmer RA. NSAID exposure and risk of Alzheimer disease: is timing everything? Neurology 2009;72(22):1884-5.
Full Text: Exclude - editorial, no primary data

Bennett DA, Wilson RS, Schneider JA, et al. Apolipoprotein E epsilon4 allele, AD pathology, and the clinical expression of Alzheimer's disease. Neurology 2003;60(2):246-52.
Full Text: Exclude - outcomes non-specific AD

Bennett DA, Wilson RS, Schneider JA, et al. Education modifies the relation of AD pathology to level of cognitive function in older persons. Neurology 2003;60(12):1909-15.
Full Text: Exclude - outcomes non-specific AD

Benton D, Williams C, Brown A. Impact of consuming a milk drink containing a probiotic on mood and cognition. Eur J Clin Nutr 2007;61(3):355-61.
Full Text: Exclude - AD/CD f/u < 1 year

Bermejo-Pareja F, Benito-Leon J, Vega S, et al. Incidence and subtypes of dementia in three elderly populations of central Spain. J Neurol Sci 2008;264(1-2):63-72.
Full Text: Exclude - incidence study (risk factor not focus of study)

Berr C, Coudray C, Bonithon-Kopp C, et al. Demographic and cardiovascular risk factors in relation to antioxidant status: the EVA Study. Int J Vitam Nutr Res 1998;68(1):26-35.
Full Text: Exclude - outcomes not AD/CD

Berr C, Richard MJ, Gourlet V, et al. Enzymatic antioxidant balance and cognitive decline in aging--the EVA study. Eur J Epidemiol 2004;19(2):133-8.
Full Text: Exclude - risk factor out of scope

Berr C, Richard MJ, Roussel AM, et al. Systemic oxidative stress and cognitive performance in the population-based EVA study. Etude du Vieillissement Arteriel. Free Radic Biol Med 1998;24(7-8):1202-8.
Full Text: Exclude - not longitudinal

Bes A, Orgogozo JM, Poncet M, et al. A 24-month, double-blind, placebo-controlled multicentre pilot study of the efficacy and safety of nicergoline 60 mg per day in elderly hypertensive patients with leukoaraiosis. Eur J Neurol 1999;6(3):313-22.
Full Text: Exclude - risk factor out of scope

Bicikova M, Ripova D, Hill M, et al. Plasma levels of 7-

hydroxylated dehydroepiandrosterone (DHEA) metabolites and selected amino-thiols as discriminatory tools of Alzheimer's disease and vascular dementia. Clin Chem Lab Med 2004;42(5):518-24.
Full Text: Exclude - dementia @ baseline

Bierman EJ, Comijs HC, Jonker C, et al. Effects of anxiety versus depression on cognition in later life. Am J Geriatr Psychiatry 2005;13(8):686-93.
Full Text: Exclude - not longitudinal

Bird AS, Blizard RA, Mann AH. Treating hypertension in the older person: an evaluation of the association of blood pressure level and its reduction with cognitive performance. J Hypertens 1990;8(2):147-52.
Full Text: Exclude - AD/CD f/u < 1 yr

Birns J, Morris R, Jarosz J, et al. The structural and functional consequences of diurnal variations in blood pressure in treated patients with hypertensive cerebrovascular disease. J Hypertens 2009;27(5):1042-8.
Full Text: Exclude - observational N<300

Bisol Balardin J, Vedana G, Ludwig A, et al. Contextual memory and encoding strategies in young and older adults with and without depressive symptoms. Aging Ment Health 2009;13(3):313-8.
Full Text: Exclude - observational N<300

Blasko I, Jungwirth S, Jellinger K, et al. Effects of medications on plasma amyloid beta (Abeta) 42: longitudinal data from the VITA cohort. J Psychiatr Res 2008;42(11):946-55.
Full Text: Exclude - dementia @ baseline

Blasko I, Kemmler G, Krampla W, et al. Plasma amyloid beta protein 42 in non-demented persons aged 75 years: effects of concomitant medication and medial temporal lobe atrophy. Neurobiol Aging 2005;26(8):1135-43.
Full Text: Exclude - risk factor out of scope

Bogner HR, Richie MB, de Vries HF, et al. Depression, cognition, apolipoprotein e genotype: latent class approach to identifying subtype. Am J Geriatr Psychiatry 2009;17(4):344-52.
Full Text: Exclude - not longitudinal

Bohannon AD, Fillenbaum GG, Pieper CF, et al. Relationship of race/ethnicity and blood pressure to change in cognitive function. J Am Geriatr Soc 2002;50(3):424-9.
Full Text: Exclude - SPMSQ single test

Boita F, Couderc LJ, Crestani B, et al. [Evaluation of pulmonary function in the elderly. Intergroupe Pneumo Geriatrie SPLF-SFGG]. Rev Mal Respir 2006;23(6):619-28.
Full Text: Exclude: non-English

Boland LL, Shahar E, Iber C, et al. Measures of cognitive function in persons with varying degrees of sleep-disordered breathing: the Sleep Heart Health Study. J Sleep Res 2002;11(3):265-72.
Full Text: Exclude - not longitudinal

Bond GE, Burr RL, McCurry SM, et al. Alcohol and cognitive performance: a longitudinal study of older Japanese Americans. The Kame Project. Int Psychogeriatr 2005;17(4):653-68.
Full Text: Exclude - risk factor out of scope

Boritz TZ, Angus L, Monette G, et al. An empirical analysis of autobiographical memory specificity subtypes in brief emotion-focused and client-centered treatments of depression. Psychother Res 2008;18(5):584-93.
Full Text: Exclude - risk factor out of scope

Boron JB, Turiano NA, Willis SL, et al. Effects of cognitive training on change in accuracy in inductive reasoning ability. J Gerontol B Psychol Sci Soc Sci 2007;62(3):P179-86.
Full Text: Exclude - AD/CD f/u < 1 year

Boron JB, Willis SL, Schaie KW. Cognitive training gain as a predictor of mental status. J Gerontol B Psychol Sci Soc Sci 2007;62(1):P45-52.
Full Text: Exclude - comparator not placebo/control

Bosch J, Yusuf S, Pogue J, et al. Use of ramipril in preventing stroke: double blind randomised trial. BMJ 2002;324(7339):699-702.
Full Text: Exclude - outcomes not AD/CD

Bosch J, Yusuf S, Pogue J, et al. Use of ramipril in preventing stroke: double blind randomised trial.[see comment][summary for patients in J Fam Pract. 2002 Jul;51(7):595; PMID: 12160488]. BMJ 2002;324(7339):699-702.
Full Text: Exclude - outcomes unacceptably assessed

Bottiggi KA, Salazar JC, Yu L, et al. Long-term cognitive impact of anticholinergic medications in older adults. Am J Geriatr Psychiatry 2006;14(11):980-4.
Full Text: Exclude - risk factor out of scope

Bouchard M, Mergler D, Baldwin M, et al. Neurobehavioral functioning after cessation of manganese exposure: a follow-up after 14 years. Am J Ind Med 2007;50(11):831-40.
Full Text: Exclude - observational N < 300

Brady CB, Gaziano JM, Cxypoliski RA, et al. Homocysteine lowering and cognition in CKD: the Veterans Affairs homocysteine study. Am J Kidney Dis 2009;54(3):440-9.
Full Text: Exclude - not applicable population

Brady CB, Spiro A, 3rd, Gaziano JM. Effects of age and hypertension status on cognition: the Veterans Affairs Normative Aging Study. Neuropsychology 2005;19(6):770-7.
Full Text: Exclude - not longitudinal

Braszko JJ, Karwowska-Polecka W, Halicka D, et al. Captopril and enalapril improve cognition and depressed

mood in hypertensive patients. J Basic Clin Physiol Pharmacol 2003;14(4):323-43.
Full Text: Exclude - observational N < 300

Brayne C, Best N, Muir M, et al. Five-year incidence and prediction of dementia and cognitive decline in a population sample of women aged 70-79 at baseline. Int J Geriatr Psychiatry 1997;12(11):1107-18.
Full Text: Exclude - observational N<300

Brayne C, Gao L, Dewey M, et al. Dementia before death in ageing societies--the promise of prevention and the reality. PLoS Med 2006;3(10):e397.
Full Text: Exclude - dementia @ baseline

Brehaut JC, Raina P, Lindsay J. Does cognitive status modify the relationship between education and mortality? Evidence from the Canadian Study of Health and Aging. Int Psychogeriatr 2004;16(1):75-91.
Full Text: Exclude - dementia @ baseline

Breitner JC, Welsh KA, Helms MJ, et al. Delayed onset of Alzheimer's disease with nonsteroidal anti-inflammatory and histamine H2 blocking drugs. Neurobiol Aging 1995;16(4):523-30.
Full Text: Exclude - dementia @ baseline

Broe GA, Creasey H, Jorm AF, et al. Health habits and risk of cognitive impairment and dementia in old age: a prospective study on the effects of exercise, smoking and alcohol consumption. Aust N Z J Public Health 1998;22(5):621-3.
Full Text: Exclude - no outcomes data

Broe GA, Grayson DA, Creasey HM, et al. Anti-inflammatory drugs protect against Alzheimer disease at low doses. Arch Neurol 2000;57(11):1586-91.
Full Text: Exclude - not longitudinal

Brown DR, Wang Y, Ward A, et al. Chronic psychological effects of exercise and exercise plus cognitive strategies. Med Sci Sports Exerc 1995;27(5):765-75.
Full Text: Exclude - risk factor out of scope

Brown ES, Vera E, Frol AB, et al. Effects of chronic prednisone therapy on mood and memory. J Affect Disord 2007;99(1-3):279-83.
Full Text: Exclude - not applicable population

Bruce DG, Davis WA, Casey GP, et al. Predictors of cognitive decline in older individuals with diabetes. Diabetes Care 2008;31(11):2103-7.
Full Text: Exclude - observational N<300

Bruce DG, Davis WA, Casey GP, et al. Predictors of cognitive impairment and dementia in older people with diabetes. Diabetologia 2008;51(2):241-8.
Full Text: Exclude - <60% of dementia is AD

Bruehl H, Wolf OT, Sweat V, et al. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. Brain Res 2009;1280:186-94.
Full Text: Exclude - observational N<300

Buchman AS, Wilson RS, Boyle PA, et al. Grip strength and the risk of incident Alzheimer's disease. Neuroepidemiology 2007;29(1-2):66-73.
Full Text: Exclude - risk factor out of scope

Burke V, Beilin LJ, Cutt HE, et al. Moderators and mediators of behaviour change in a lifestyle program for treated hypertensives: a randomized controlled trial (ADAPT). Health Educ Res 2008;23(4):583-91.
Full Text: Exclude - risk factor out of scope

Burke V, Mansour J, Mori TA, et al. Changes in cognitive measures associated with a lifestyle program for treated hypertensives: a randomized controlled trial (ADAPT). Health Educ Res 2008;23(2):202-17.
Full Text: Exclude - risk factor out of scope

Butler SM, Ashford JW, Snowdon DA. Age, education, and changes in the Mini-Mental State Exam scores of older women: findings from the Nun Study. J Am Geriatr Soc 1996;44(6):675-81.
Full Text: Exclude - likely dementia @ baseline

Bygren LO, Weissglas G, Wikstrom BM, et al. Cultural participation and health: a randomized controlled trial among medical care staff. Psychosom Med 2009;71(4):469-73.
Full Text: Exclude - <80% >= 50 yr old

Cancelli I, Gigli GL, Piani A, et al. Drugs with anticholinergic properties as a risk factor for cognitive impairment in elderly people: a population-based study. J Clin Psychopharmacol 2008;28(6):654-9.
Full Text: Exclude - risk factor out of scope

Cao YJ, Mager DE, Simonsick EM, et al. Physical and cognitive performance and burden of anticholinergics, sedatives, and ACE inhibitors in older women. Clin Pharmacol Ther 2008;83(3):422-9.
Full Text: Exclude - risk factor out of scope

Capurso C, Solfrizzi V, D'Introno A, et al. Short arm of chromosome 11 and sporadic Alzheimer's disease: catalase and cathepsin D gene polymorphisms. Neurosci Lett 2008;432(3):237-42.
Full Text: Exclude - dementia @ baseline

Carles S, Jr., Curnier D, Pathak A, et al. Effects of short-term exercise and exercise training on cognitive function among patients with cardiac disease. J Cardiopulm Rehabil Prev 2007;27(6):395-9.
Full Text: Exclude - RCT N<50

Carlson LE, Sherwin BB. Relationships among cortisol (CRT), dehydroepiandrosterone-sulfate (DHEAS), and memory in a longitudinal study of healthy elderly men and women. Neurobiol Aging 1999;20(3):315-24.
Full Text: Exclude - risk factor out of scope

Carlsson C, Gleason C, Hess T, et al. Effects of simvastatin on cerebrospinal fluid biomarkers and cognition in middle-aged adults at risk for Alzheimer's disease. J Alzheimers Dis 2008;13(2):187-97.
Full Text: Exclude - not longitudinal

Carlsson CM, Papcke-Benson K, Carnes M, et al. Health-related quality of life and long-term therapy with pravastatin and tocopherol (vitamin E) in older adults. Drugs Aging 2002;19(10):793-805.
Full Text: Exclude - AD/CD f/u < 1 year

Carriere I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Arch Intern Med 2009;169(14):1317-24.
Full Text: Exclude - risk factor out of scope

Cascalheira JF, Joao SS, Pinhancos SS, et al. Serum homocysteine: interplay with other circulating and genetic factors in association to Alzheimer's type dementia. Clin Biochem 2009;42(9):783-90.
Full Text: Exclude - observational N<300

Caselli RJ, Reiman EM, Osborne D, et al. Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE e4 allele. Neurology 2004;62(11):1990-5.
Full Text: Exclude - observational N<300

Caserta RJ, Young J, Janelle CM. Old dogs, new tricks: training the perceptual skills of senior tennis players. J Sport Exerc Psychol 2007;29(4):479-97.
Full Text: Exclude - risk factor out of scope

Cassidy K, Kotynia-English R, Acres J, et al. Association between lifestyle factors and mental health measures among community-dwelling older women. Aust N Z J Psychiatry 2004;38(11-12):940-7.
Full Text: Exclude - not longitudinal

Censori B, Manara O, Agostinis C, et al. Dementia after first stroke. Stroke 1996;27(7):1205-10.
Full Text: Exclude - not applicable population

Cervilla JA, Prince M, Joels S, et al. Long-term predictors of cognitive outcome in a cohort of older people with hypertension. Br J Psychiatry 2000;177:66-71.
Full Text: Exclude - not longitudinal

Cervilla JA, Prince M, Joels S, et al. Does depression predict cognitive outcome 9 to 12 years later? Evidence from a prospective study of elderly hypertensives. Psychol Med 2000;30(5):1017-23.
Full Text: Exclude - Inadequate outcomes

Chaves ML, Camozzato AL, Godinho C, et al. Incidence of mild cognitive impairment and Alzheimer disease in Southern Brazil. J Geriatr Psychiatry Neurol 2009;22(3):181-7.
Full Text: Exclude - non-Western country

Chen R, Hu Z, Wei L, et al. Is the relationship between syndromes of depression and dementia temporal? The MRC-ALPHA and Hefei-China studies. Psychol Med 2009;39(3):425-30.
Full Text: Exclude - dementia @ baseline

Cherubini A, Andres-Lacueva C, Martin A, et al. Low plasma N-3 fatty acids and dementia in older persons: the InCHIANTI study. J Gerontol A Biol Sci Med Sci 2007;62(10):1120-6.
Full Text: Exclude - not longitudinal

Cherubini A, Martin A, Andres-Lacueva C, et al. Vitamin E levels, cognitive impairment and dementia in older persons: the InCHIANTI study. Neurobiol Aging 2005;26(7):987-94.
Full Text: Exclude - not longitudinal

Chiang CJ, Yip PK, Wu SC, et al. Midlife risk factors for subtypes of dementia: a nested case-control study in Taiwan. Am J Geriatr Psychiatry 2007;15(9):762-71.
Full Text: Exclude - inadequate AD assessment

Chiu CC, Su KP, Cheng TC, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(6):1538-44.
Full Text: Exclude - RCT N<50

Chodosh J, Kado DM, Seeman TE, et al. Depressive symptoms as a predictor of cognitive decline: MacArthur Studies of Successful Aging. Am J Geriatr Psychiatry 2007;15(5):406-15.
Full Text: Exclude - SPMSQ single test

Christensen H, Jorm AF, Henderson AS, et al. The relationship between health and cognitive functioning in a sample of elderly people in the community. Age Ageing 1994;23(3):204-12.
Full Text: Exclude - not longitudinal

Christensen H, Korten A, Jorm AF, et al. Activity levels and cognitive functioning in an elderly community sample. Age Ageing 1996;25(1):72-80.
Full Text: Exclude - not longitudinal

Chui MH, Papanikolaou Y, Fontaine-Bisson B, et al. The TNF-alpha-238G > a single-nucleotide polymorphism protects against memory decline in older adults with type 2 diabetes. Behav Neurosci 2007;121(3):619-24.
Full Text: Exclude - observational N<300

Churchill JD, Galvez R, Colcombe S, et al. Exercise, experience and the aging brain. Neurobiol Aging 2002;23(5):941-55.
Full Text: Exclude - observational N<300

Clark MS, Bond MJ, Hecker JR. Environmental stress, psychological stress and allostatic load. Psychol Health Med 2007;12(1):18-30.
Full Text: Exclude - not applicable population

Clarke R, Harrison G, Richards S. Effect of vitamins and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. J Intern Med 2003;254(1):67-75.
Full Text: Exclude - not applicable population

Clarke R, Sherliker P, Hin H, et al. Folate and vitamin B12 status in relation to cognitive impairment and anaemia in the setting of voluntary fortification in the UK. Br J Nutr 2008;100(5):1054-9.
Full Text: Exclude - risk factor out of scope

Clarke R, Smith AD, Jobst KA, et al. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol 1998;55(11):1449-55.
Full Text: Exclude - dementia @ baseline

Clarkson-Smith L, Hartley AA. Relationships between physical exercise and cognitive abilities in older adults. Psychol Aging 1989;4(2):183-9.
Full Text: Exclude - not longitudinal

Cohen-Zion M, Stepnowsky C, Marler, et al. Changes in cognitive function associated with sleep disordered breathing in older people. J Am Geriatr Soc 2001;49(12):1622-7.
Full Text: Exclude - observational N < 300

Colcombe SJ, Kramer AF, Erickson KI, et al. Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A 2004;101(9):3316-21.
Full Text: Exclude - outcome non-specified AD

Comijs HC, Dik MG, Deeg DJ, et al. The course of cognitive decline in older persons: results from the longitudinal aging study amsterdam. Dement Geriatr Cogn Disord 2004;17(3):136-42.
Full Text: Exclude - observational N<300

Comijs HC, Jonker C, Beekman AT, et al. The association between depressive symptoms and cognitive decline in community-dwelling elderly persons. Int J Geriatr Psychiatry 2001;16(4):361-7.
Full Text: Exclude - Q2 Continuous data only

Comijs HC, van Tilburg T, Geerlings SW, et al. Do severity and duration of depressive symptoms predict cognitive decline in older persons? Results of the Longitudinal Aging Study Amsterdam. Aging Clin Exp Res 2004;16(3):226-32.
Full Text: Exclude - observational N<300

Conquer JA, Tierney MC, Zecevic J, et al. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. Lipids 2000;35(12):1305-12.
Full Text: Exclude - dementia @ baseline

Corder EH, Beaumont H. Susceptibility groups for Alzheimer's disease (OPTIMA cohort): integration of gene variants and biochemical factors. Mech Ageing Dev 2007;128(1):76-82.
Full Text: Exclude - not longitudinal

Cordonnier C, van der Flier WM, Sluimer JD, et al. Prevalence and severity of microbleeds in a memory clinic setting. Neurology 2006;66(9):1356-60.
Full Text: Exclude - dementia @ baseline

Correa Leite ML, Nicolosi A, Cristina S, et al. Nutrition and cognitive deficit in the elderly: a population study. Eur J Clin Nutr 2001;55(12):1053-8.
Full Text: Exclude - not longitudinal

Corsentino EA, Sawyer K, Sachs-Ericsson N, et al. Depressive symptoms moderate the influence of the apolipoproteine epsilon4 allele on cognitive decline in a sample of community dwelling older adults. Am J Geriatr Psychiatry 2009;17(2):155-65.
Full Text: Exclude - SPMSQ single test

Corzo L, Zas R, Rodriguez S, et al. Decreased levels of serum nitric oxide in different forms of dementia. Neurosci Lett 2007;420(3):263-7.
Full Text: Exclude - dementia @ baseline

Costa MM, Reus VI, Wolkowitz OM, et al. Estrogen replacement therapy and cognitive decline in memory-impaired post-menopausal women. Biol Psychiatry 1999;46(2):182-8.
Full Text: Exclude - dementia @ baseline

Cramer C, Haan M, Galea S, et al. Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. Neurology 2008;71(5):344-50.
Full Text: Exclude - outcome non-specific AD

Crooks VC, Lubben J, Petitti DB, et al. Social network, cognitive function, and dementia incidence among elderly women. Am J Public Health 2008;98(7):1221-7.
Full Text: Exclude - <60% of dementia is AD

Crowe M, Andel R, Pedersen NL, et al. Do work-related stress and reactivity to stress predict dementia more than 30 years later? Alzheimer Dis Assoc Disord 2007;21(3):205-9.
Full Text: Exclude - <60% of dementia is AD

Csernansky JG, Dong H, Fagan AM, et al. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am J Psychiatry 2006;163(12):2164-9.
Full Text: Exclude - dementia @ baseline

Cui X, Lyness JM, Tu X, et al. Does depression precede or follow executive dysfunction? Outcomes in older primary care patients. Am J Psychiatry 2007;164(8):1221-8.
Full Text: Exclude - observational N<300

Cukierman-Yaffe T, Gerstein HC, Anderson C, et al. Glucose intolerance and diabetes as risk factors for cognitive impairment in people at high cardiovascular risk: results from the ONTARGET/TRANSCEND research programme. Diabetes Res Clin Pract 2009;83(3):387-93.
Full Text: Exclude - not longitudinal

Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. Diabetes Care 2009;32(2):221-6.
Full Text: Exclude - not longitudinal

Cummings SR, Black DM, Nevitt MC, et al. Appendicular bone density and age predict hip fracture in women. The Study of Osteoporotic Fractures Research Group.[see comment]. JAMA 1990;263(5):665-8.
Full Text: Exclude - outcomes not AD/CD

Cunningham CJ, Sinnott M, Denihan A, et al. Endogenous sex hormone levels in postmenopausal women with Alzheimer's disease. J Clin Endocrinol Metab 2001;86(3):1099-103.
Full Text: Exclude - dementia @ baseline

Dahle CL, Jacobs BS, Raz N. Aging, vascular risk, and cognition: blood glucose, pulse pressure, and cognitive performance in healthy adults. Psychol Aging 2009;24(1):154-62.
Full Text: Exclude - observational N<300

Dam H. Depression in stroke patients 7 years following stroke. Acta Psychiatr Scand 2001;103(4):287-93.
Full Text: Exclude - not applicable population

Dangour AD, Allen E, Elbourne D, et al. Fish consumption and cognitive function among older people in the UK: baseline data from the OPAL study. J Nutr Health Aging 2009;13(3):198-202.
Full Text: Exclude - not longitudinal

Dargent-Molina P, Favier F, Grandjean H, et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study.[erratum appears in Lancet 1996 Aug 10;348(9024):416]. Lancet 1996;348(9021):145-9.
Full Text: Exclude - outcomes not AD/CD

Dartigues JF, Carcaillon L, Helmer C, et al. Vasodilators and nootropics as predictors of dementia and mortality in the PAQUID cohort. J Am Geriatr Soc 2007;55(3):395-9.
Full Text: Exclude - <60% of dementia is AD

Dartigues JF, Gagnon M, Barberger-Gateau P, et al. The Paquid epidemiological program on brain ageing. Neuroepidemiology 1992;11 Suppl 1:14-8.
Full Text: Exclude - methods paper

Dassanayake T, Gawarammana IB, Weerasinghe V, et al. Auditory event-related potential changes in chronic occupational exposure to organophosphate pesticides. Clin Neurophysiol 2009;120(9):1693-8.
Full Text: Exclude - non-Western country

de Castro MS, Fuchs FD, Santos MC, et al. Pharmaceutical care program for patients with uncontrolled hypertension. Report of a double-blind clinical trial with ambulatory blood pressure monitoring. Am J Hypertens 2006;19(5):528-33.
Full Text: Exclude - non-Western country

De Ronchi D, Fratiglioni L, Rucci P, et al. The effect of education on dementia occurrence in an Italian population with middle to high socioeconomic status. Neurology 1998;50(5):1231-8.
Full Text: Exclude - not longitudinal

Dealberto MJ, Pajot N, Courbon D, et al. Breathing disorders during sleep and cognitive performance in an older community sample: the EVA Study. J Am Geriatr Soc 1996;44(11):1287-94.
Full Text: Exclude - not longitudinal

Dealberto MJ, Sauron B, Derouesne C, et al. Factors associated with low cognitive performance in general practice. Eur Arch Psychiatry Clin Neurosci 1994;244(2):53-8.
Full Text: Exclude - not longitudinal

Deary IJ, Whalley LJ, Batty GD, et al. Physical fitness and lifetime cognitive change. Neurology 2006;67(7):1195-200.
Full Text: Exclude - not longitudinal

Deary IJ, Whiteman MC, Pattie A, et al. Apolipoprotein e gene variability and cognitive functions at age 79: a follow-up of the Scottish mental survey of 1932. Psychol Aging 2004;19(2):367-71.
Full Text: Exclude - not longitudinal

Deary IJ, Whiteman MC, Starr JM, et al. The impact of childhood intelligence on later life: following up the Scottish mental surveys of 1932 and 1947. J Pers Soc Psychol 2004;86(1):130-47.
Full Text: Exclude - methods paper

Debling D, Amelang M, Hasselbach P, et al. Diabetes and cognitive function in a population-based study of elderly women and men. J Diabetes Complications 2006;20(4):238-45.
Full Text: Exclude - not longitudinal

DeCarli C, Miller BL, Swan GE, et al. Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung, and Blood Institute Twin Study. Arch Neurol 2001;58(4):643-7.
Full Text: Exclude - outcomes non-specific AD

DeCarli C, Mungas D, Harvey D, et al. Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. Neurology 2004;63(2):220-7.
Full Text: Exclude - observational N < 300

Deeg DJH, van Tilburg T, Smit JH, et al. Attrition in the Longitudinal Aging Study Amsterdam. The effect of differential inclusion in side studies. J Clin Epidemiol 2002;55(4):319-28.
Full Text: Exclude - risk factor out of scope

den Heijer T, Launer LJ, Prins ND, et al. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. Neurology 2005;64(2):263-7.
Full Text: Exclude - outcomes non-specific AD

Deschamps V, Astier X, Ferry M, et al. Nutritional status of healthy elderly persons living in Dordogne, France, and relation with mortality and cognitive or functional decline. Eur J Clin Nutr 2002;56(4):305-12.
Full Text: Exclude - observational N < 300

Desmond DW, Tatemichi TK, Paik M, et al. Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. Arch Neurol 1993;50(2):162-6.
Full Text: Exclude - observational N<300

desRosiers G, Hodges JR, Berrios G. The neuropsychological differentiation of patients with very mild Alzheimer's disease and/or major depression. J Am Geriatr Soc 1995;43(11):1256-63.
Full Text: Exclude - dementia @ baseline

Devi G, Massimi S, Schultz S, et al. A double-blind, placebo-controlled trial of donepezil for the treatment of menopause-related cognitive loss. Gender Medicine 2007;4(4):352-8.
Full Text: Exclude - RCT N<50

Devore EE, Stampfer MJ, Breteler MM, et al. Dietary fat intake and cognitive decline in women with type 2 diabetes. Diabetes Care 2009;32(4):635-40.
Full Text: Exclude - dementia @ baseline

Di Bari M, Pahor M, Franse LV, et al. Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. Am J Epidemiol 2001;153(1):72-8.
Full Text: Exclude - not cognitive outcomes

Di Bari M, Salti F, Nardi M, et al. Undertreatment of hypertension in community-dwelling older adults: a drug-utilization study in Dicomano, Italy. J Hypertens 1999;17(11):1633-40.
Full Text: Exclude - not longitudinal

Diener HC, Sacco RL, Yusuf S, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. Lancet Neurol 2008;7(10):875-84.
Full Text: Exclude - risk factor out of scope

Dik M, Deeg DJ, Visser M, et al. Early life physical activity and cognition at old age. J Clin Exp Neuropsychol 2003;25(5):643-53.
Full Text: Exclude - not longitudinal

Dik MG, Jonker C, Comijs HC, et al. Contribution of metabolic syndrome components to cognition in older individuals. Diabetes Care 2007;30(10):2655-60.
Full Text: Exclude - not longitudinal

Dik MG, Jonker C, Hack CE, et al. Serum inflammatory proteins and cognitive decline in older persons. Neurology 2005;64(8):1371-7.
Full Text: Exclude - risk factor out of scope

Doll R, Peto R, Boreham J, et al. Smoking and dementia in male British doctors: prospective study. BMJ 2000;320(7242):1097-102.
Full Text: Exclude - outcomes non-specific AD

Doraiswamy P, Steffens D, McQuoid D. Statin use and hippocampal volumes in elderly subjects at risk for Alzheimer's disease: a pilot observational study. Am J Alzheimers Dis Other Demen 2004;19(5):275-8.
Full Text: Exclude - not longitudinal

Dorner T, Kranz A, Zettl-Wiedner K, et al. The effect of structured strength and balance training on cognitive function in frail, cognitive impaired elderly long-term care residents. Aging Clin Exp Res 2007;19(5):400-5.
Full Text: Exclude - selected population

Dotson VM, Resnick SM, Zonderman AB. Differential association of concurrent, baseline, and average depressive symptoms with cognitive decline in older adults. Am J Geriatr Psychiatry 2008;16(4):318-30.
Full Text: Exclude - Q2 continuous data only

Downhill JE, Jr., Robinson RG. Longitudinal assessment of depression and cognitive impairment following stroke. J Nerv Ment Dis 1994;182(8):425-31.
Full Text: Exclude - not applicable population

Draper K, Ponsford J. Cognitive functioning ten years following traumatic brain injury and rehabilitation. Neuropsychology 2008;22(5):618-25.
Full Text: Exclude - <80% >= 50 yo

Dufouil C, Alperovitch A, Tzourio C. Influence of education on the relationship between white matter lesions and cognition. Neurology 2003;60(5):831-6.
Full Text: Exclude - risk factor out of scope

Dufouil C, Ducimetiere P, Alperovitch A. Sex differences in the association between alcohol consumption and cognitive performance. EVA Study Group. Epidemiology of Vascular Aging. Am J Epidemiol 1997;146(5):405-12.
Full Text: Exclude - not longitudinal

Dufouil C, Richard F, Fievet N, et al. APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: the Three-City Study. Neurology 2005;64(9):1531-8.
Full Text: Exclude - dementia @ baseline

Dunne MP, Macdonald D, Hartley LR. The effects of nicotine upon memory and problem solving performance. Physiol Behav 1986;37(6):849-54.
Full Text: Exclude - <80% >= 50 yo

Edelstein SL, Kritz-Silverstein D, Barrett-Connor E. Prospective association of smoking and alcohol use with cognitive function in an elderly cohort. J Womens Health 1998;7(10):1271-81.
Full Text: Exclude - outcome non-specific AD

Elias MF, Elias PK, Sullivan LM, et al. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. Int J Obes Relat Metab Disord 2003;27(2):260-8.
Full Text: Exclude - not longitudinal

Elias MF, Elias PK, Sullivan LM, et al. Obesity, diabetes and cognitive deficit: The Framingham Heart Study. Neurobiol Aging 2005;26 Suppl 1:11-6.
Full Text: Exclude - not longitudinal

Elias MF, Robbins MA, Budge MM, et al. Arterial pulse wave velocity and cognition with advancing age. Hypertension 2009;53(4):668-73.
Full Text: Exclude - Risk factor out of scope

Elias MF, Robbins MA, Elias PK, et al. A longitudinal study of blood pressure in relation to performance on the Wechsler Adult Intelligence Scale. Health Psychol 1998;17(6):486-93.
Full Text: Exclude - observational N<300

Elias MF, Sullivan LM, D'Agostino RB, et al. Framingham stroke risk profile and lowered cognitive performance. Stroke 2004;35(2):404-9.
Full Text: Exclude - risk factor out of scope

Elias MF, Sullivan LM, D'Agostino RB, et al. Homocysteine and cognitive performance in the Framingham offspring study: age is important. Am J Epidemiol 2005;162(7):644-53.
Full Text: Exclude - not longitudinal

Elias MF, Sullivan LM, Elias PK, et al. Left ventricular mass, blood pressure, and lowered cognitive performance in the Framingham offspring. Hypertension 2007;49(3):439-45.
Full Text: Exclude - risk factor out of scope

Elias MF, Wolf PA, D'Agostino RB, et al. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. Am J Epidemiol 1993;138(6):353-64.
Full Text: Exclude - not longitudinal

Elias PK, Elias MF, D'Agostino RB, et al. NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. Diabetes Care 1997;20(9):1388-95.
Full Text: Exclude - not longitudinal

Elias PK, Elias MF, Robbins MA, et al. Blood pressure-related cognitive decline: does age make a difference? Hypertension 2004;44(5):631-6.
Full Text: Exclude - risk factor out of scope

Elkins JS, Johnston SC, Ziv E, et al. Methylenetetrahydrofolate reductase C677T polymorphism and cognitive function in older women. Am J Epidemiol 2007;166(6):672-8.
Full Text: Exclude - risk factor out of scope

Elkins JS, Yaffe K, Cauley JA, et al. Pre-existing hypertension and the impact of stroke on cognitive function. Ann Neurol 2005;58(1):68-74.
Full Text: Exclude - observational N<300

Emery CF, Shermer RL, Hauck ER, et al. Cognitive and psychological outcomes of exercise in a 1-year follow-up study of patients with chronic obstructive pulmonary disease. Health Psychol 2003;22(6):598-604.
Full Text: Exclude - RCT N<50

Engelhart MJ, Ruitenberg A, Meijer J, et al. Plasma levels of antioxidants are not associated with Alzheimer's disease or cognitive decline. Dement Geriatr Cogn Disord 2005;19(2-3):134-9.
Full Text: Exclude - not longitudinal

Eskelinen MH, Ngandu T, Helkala EL, et al. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. Int J Geriatr Psychiatry 2008;23(7):741-7.
Full Text: Exclude - Not adequate reference standard

Euser SM, Hofman A, Westendorp RG, et al. Serum uric acid and cognitive function and dementia. Brain 2009;132(Pt 2):377-82.
Full Text: Exclude - risk factor out of scope

Euser SM, van Bemmel T, Schram MT, et al. The effect of age on the association between blood pressure and cognitive function later in life. J Am Geriatr Soc 2009;57(7):1232-7.
Full Text: Exclude - AD/CD f/u < 1 year

Eussen SJ, de Groot LC, Joosten LW, et al. Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: a randomized, placebo-controlled trial. Am J Clin Nutr 2006;84(2):361-70.
Full Text: Exclude - not applicable population

Eussen SJ, Ferry M, Hininger I, et al. Five year changes in mental health and associations with vitamin B12/folate status of elderly Europeans. J Nutr Health Aging 2002;6(1):43-50.
Full Text: Exclude - observational N<300

Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. Pharmacotherapy 2009;29(7):800-11.
Full Text: Exclude - not applicable population

Fabrigoule C, Letenneur L, Dartigues JF, et al. Social and leisure activities and risk of dementia: a prospective longitudinal study.[see comment]. J Am Geriatr Soc

1995;43(5):485-90.
Full Text: Exclude - <60% of dementia is AD

Farmer ME, Kittner SJ, Abbott RD, et al. Longitudinally measured blood pressure, antihypertensive medication use, and cognitive performance: the Framingham Study. J Clin Epidemiol 1990;43(5):475-80.
Full Text: Exclude - not longitudinal

Farmer ME, Kittner SJ, Rae DS, et al. Education and change in cognitive function. The Epidemiologic Catchment Area Study. Ann Epidemiol 1995;5(1):1-7.
Full Text: Exclude - dementia @ baseline

Farmer ME, White LR, Kittner SJ, et al. Neuropsychological test performance in Framingham: a descriptive study. Psychol Rep 1987;60(3 Pt 2):1023-40.
Full Text: Exclude - not longitudinal

Faxen-Irving G, Andren-Olsson B, Geijerstam A, et al. Nutrition education for care staff and possible effects on nutritional status in residents of sheltered accommodation. Eur J Clin Nutr 2005;59(8):947-54.
Full Text: Exclude - selected population

Fernandes MA, Proenca MT, Nogueira AJ, et al. Influence of apolipoprotein E genotype on blood redox status of Alzheimer's disease patients. Int J Mol Med 1999;4(2):179-86.
Full Text: Exclude - dementia @ baseline

File SE, Hartley DE, Elsabagh S, et al. Cognitive improvement after 6 weeks of soy supplements in postmenopausal women is limited to frontal lobe function. Menopause 2005;12(2):193-201.
Full Text: Exclude - AD/CD f/u < 1 yr

Finkel D, Andel R, Gatz M, et al. The role of occupational complexity in trajectories of cognitive aging before and after retirement. Psychol Aging 2009;24(3):563-73.
Full Text: Exclude - risk factor out of scope (occupational complexity)

Finkel D, Reynolds CA, McArdle JJ, et al. The longitudinal relationship between processing speed and cognitive ability: genetic and environmental influences. Behav Genet 2005;35(5):535-49.
Full Text: Exclude - risk factor out of scope

Fiocco AJ, Poirier J, Joober R, et al. Acute and long-term associations between ApoE genetic polymorphism, cortisol levels, and declarative memory performance in older adults. Psychoneuroendocrinology 2008;33(5):625-33.
Full Text: Exclude - observational N<300

Fischer P, Zehetmayer S, Bauer K, et al. Relation between vascular risk factors and cognition at age 75. Acta Neurol Scand 2006;114(2):84-90.
Full Text: Exclude - not longitudinal

Fitzpatrick AL, Buchanan CK, Nahin RL, et al. Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons. J Gerontol A Biol Sci Med Sci 2007;62(11):1244-51.
Full Text: Exclude - risk factor out of scope

Fleisher AS, Sowell BB, Taylor C, et al. Clinical predictors of progression to Alzheimer disease in amnestic mild cognitive impairment. Neurology 2007;68(19):1588-95.
Full Text: Exclude - risk factor out of scope

Fletcher AE, Battersby C, Adnitt P, et al. Quality of life on antihypertensive therapy: a double-blind trial comparing quality of life on pinacidil and nifedipine in combination with a thiazide diuretic. European Pinacidil Study Group. J Cardiovasc Pharmacol 1992;20(1):108-14.
Full Text: Exclude - risk factor out of scope

Fluck E, File SE, Rymer J. Cognitive effects of 10 years of hormone-replacement therapy with tibolone. J Clin Psychopharmacol 2002;22(1):62-7.
Full Text: Exclude - observational N<300

Fogari R, Mugellini A, Zoppi A, et al. Influence of losartan and atenolol on memory function in very elderly hypertensive patients. J Hum Hypertens 2003;17(11):781-5.
Full Text: Exclude - AD/CD f/u < 1 yr

Fogari R, Mugellini A, Zoppi A, et al. Effect of telmisartan/hydrochlorothiazide vs lisinopril/hydrochlorothiazide combination on ambulatory blood pressure and cognitive function in elderly hypertensive patients. J Hum Hypertens 2006;20(3):177-85.
Full Text: Exclude - AD/CD f/u < 1 yr

Fogari R, Mugellini A, Zoppi A, et al. Effects of valsartan compared with enalapril on blood pressure and cognitive function in elderly patients with essential hypertension. Eur J Clin Pharmacol 2004;59(12):863-8.
Full Text: Exclude - AD/CD f/u < 1 yr

Foley DJ, Masaki K, White L, et al. Sleep-disordered breathing and cognitive impairment in elderly Japanese-American men. Sleep 2003;26(5):596-9.
Full Text: Exclude - AD/CD f/u < 1 yr

Ford AB, Mefrouche Z, Friedland RP, et al. Smoking and cognitive impairment: a population-based study. J Am Geriatr Soc 1996;44(8):905-9.
Full Text: Exclude - SPMSQ single test

Forti P, Maioli F, Pisacane N, et al. Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment. Neurol Res 2006;28(6):625-9.
Full Text: Exclude - risk factor out of scope

Forti P, Maioli F, Pisacane N, et al. Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment (MCI). Arch Gerontol Geriatr 2007;44 Suppl 1:155-65.

Full Text: Exclude - risk factor out of scope

Fournier LR, Ryan Borchers TA, Robison LM, et al. The effects of soy milk and isoflavone supplements on cognitive performance in healthy, postmenopausal women. J Nutr Health Aging 2007;11(2):155-64.
Full Text: Exclude - AD/CD f/u < 1 yr

Frederiksen H, Gaist D, Bathum L, et al. Angiotensin I-converting enzyme (ACE) gene polymorphism in relation to physical performance, cognition and survival--a follow-up study of elderly Danish twins. Ann Epidemiol 2003;13(1):57-65.
Full Text: Exclude - not longitudinal

French LR, Schuman LM, Mortimer JA, et al. A case-control study of dementia of the Alzheimer type. Am J Epidemiol 1985;121(3):414-21.
Full Text: Exclude - dementia @ baseline

Friedland RP, Fritsch T, Smyth KA, et al. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. Proc Natl Acad Sci U S A 2001;98(6):3440-5.
Full Text: Exclude - not longitudinal

Fritsch T, Smyth KA, McClendon MJ, et al. Associations between dementia/mild cognitive impairment and cognitive performance and activity levels in youth. J Am Geriatr Soc 2005;53(7):1191-6.
Full Text: Exclude - <60% of dementia is AD

Fujishima M, Kiyohara Y. Incidence and risk factors of dementia in a defined elderly Japanese population: the Hisayama study. Ann N Y Acad Sci 2002;977:1-8.
Full Text: Exclude - not longitudinal

Gabryelewicz T, Styczynska M, Luczywek E, et al. The rate of conversion of mild cognitive impairment to dementia: predictive role of depression. Int J Geriatr Psychiatry 2007;22(6):563-7.
Full Text: Exclude - non-Western country

Gale CR, Martyn CN, Cooper C. Cognitive impairment and mortality in a cohort of elderly people. BMJ 1996;312(7031):608-11.
Full Text: Exclude - risk factor out of scope

Gallacher JE, Pickering J, Elwood PC, et al. Glucoregulation has greater impact on cognitive performance than macro-vascular disease in men with type 2 diabetes: data from the Caerphilly study. Eur J Epidemiol 2005;20(9):761-8.
Full Text: Exclude - not longitudinal

Gallo JJ, Rebok GW, Tennsted S, et al. Linking depressive symptoms and functional disability in late life. Aging Ment Health 2003;7(6):469-80.
Full Text: Exclude - risk factor out of scope

Ganguli M, Du Y, Dodge HH, et al. Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. Arch Gen Psychiatry 2006;63(2):153-60.
Full Text: Exclude - Q2 continuous data only

Ganguli M, Seaberg EC, Ratcliff GG, et al. Cognitive stability over 2 years in a rural elderly population: the MoVIES project. Neuroepidemiology 1996;15(1):42-50.
Full Text: Exclude - risk factor out of scope

Gao L, Matthews FE, Sargeant LA, et al. An investigation of the population impact of variation in HbA1c levels in older people in England and Wales: from a population based multi-centre longitudinal study. BMC Public Health 2008;8:54.
Full Text: Exclude - <60% of dementia is AD

Gao S, Jin Y, Unverzagt FW, et al. Hypertension and cognitive decline in rural elderly Chinese. J Am Geriatr Soc 2009;57(6):1051-7.
Full Text: Exclude - non-Western country

Garcia A, Haron Y, Pulman K, et al. Increases in homocysteine are related to worsening of stroop scores in healthy elderly persons: a prospective follow-up study. J Gerontol A Biol Sci Med Sci 2004;59(12):1323-7.
Full Text: Exclude - observational N<300

Gatto NM, Henderson VW, St John JA, et al. Metabolic syndrome and cognitive function in healthy middle-aged and older adults without diabetes. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2008;15(5):627-41.
Full Text: Exclude - not longitudinal

Gatz M, Reynolds CA, Fratiglioni L, et al. Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry 2006;63(2):168-74.
Full Text: Exclude - not longitudinal

Gatz M, Svedberg P, Pedersen NL, et al. Education and the risk of Alzheimer's disease: findings from the study of dementia in Swedish twins. J Gerontol B Psychol Sci Soc Sci 2001;56(5):P292-300.
Full Text: Exclude - observational N<300

Gaw A, Murray H, Brown EA. Plasma lipoprotein(a) [Lp(a)] concentrations and cardiovascular events in the elderly: evidence from the prospective study of pravastatin in the elderly at risk (PROSPER). Atherosclerosis 2005;180(2):381-8.
Full Text: Exclude - risk factor out of scope

Geerlings MI, Schmand B, Braam AW, et al. Depressive symptoms and risk of Alzheimer's disease in more highly educated older people. J Am Geriatr Soc 2000;48(9):1092-7.
Full Text: Exclude - risk factor out of scope

Geerlings MI, Schmand B, Jonker C, et al. Education and incident Alzheimer's disease: a biased association due to selective attrition and use of a two-step diagnostic procedure? Int J Epidemiol 1999;28(3):492-7.
Full Text: Exclude - methods paper

Gengo F, Cwudzinski D, Kinkel P, et al. Effects of treatment with lovastatin and pravastatin on daytime cognitive performance. Clin Cardiol 1995;18(4):209-14.
Full Text: Exclude - RCT N<50

Gerstorf D, Lovden M, Rocke C, et al. Well-being affects changes in perceptual speed in advanced old age: longitudinal evidence for a dynamic link. Dev Psychol 2007;43(3):705-18.
Full Text: Exclude - outcomes unacceptably assessed

Ghisletta P, Bickel JF, Lovden M. Does activity engagement protect against cognitive decline in old age? Methodological and analytical considerations. J Gerontol B Psychol Sci Soc Sci 2006;61(5):P253-61.
Full Text: Exclude - outcomes unacceptably assessed

Gibellato M, Moore J, Selby K, et al. Effects of lovastatin and pravastatin on cognitive function in military aircrew. Aviat Space Environ Med 2001;72(9):805-12.
Full Text: Exclude - not applicable population

Giem P, Beeson WL, Fraser GE. The incidence of dementia and intake of animal products: preliminary findings from the Adventist Health Study. Neuroepidemiology 1993;12(1):28-36.
Full Text: Exclude - risk factor out of scope

Gill SS, Anderson GM, Fischer HD, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. Arch Intern Med 2009;169(9):867-73.
Full Text: Exclude - dementia @ baseline

Gillette-Guyonnet S, Andrieu S, Nourhashemi F, et al. Cognitive impairment and composition of drinking water in women: findings of the EPIDOS Study. Am J Clin Nutr 2005;81(4):897-902.
Full Text: Exclude - outcomes inadequately assessed

Glaso M, Nordbo G, Diep L, et al. Reduced concentrations of several vitamins in normal weight patients with late-onset dementia of the Alzheimer type without vascular disease. J Nutr Health Aging 2004;8(5):407-13.
Full Text: Exclude - observational N<300

Glei DA, Landau DA, Goldman N, et al. Participating in social activities helps preserve cognitive function: an analysis of a longitudinal, population-based study of the elderly. Int J Epidemiol 2005;34(4):864-71.
Full Text: Exclude - outcomes unacceptably assessed

Gliebus G, Lippa CF. The influence of beta-blockers on delayed memory function in people with cognitive impairment. Am J Alzheimers Dis Other Demen 2007;22(1):57-61.
Full Text: Exclude - no placebo comparator

Gluck MA, Myers CE, Nicolle MM, et al. Computational models of the hippocampal region: implications for prediction of risk for Alzheimer's disease in non-demented elderly. Curr Alzheimer Res 2006;3(3):247-57.
Full Text: Exclude - risk factor out of scope

Gold DP, Andres D, Etezadi J, et al. Structural equation model of intellectual change and continuity and predictors of intelligence in older men.[erratum appears in Psychol Aging 1998 Sep;13(3):434]. Psychol Aging 1995;10(2):294-303.
Full Text: Exclude - not longitudinal

Goldbourt U, Schnaider-Beeri M, Davidson M. Socioeconomic status in relationship to death of vascular disease and late-life dementia. J Neurol Sci 2007;257(1-2):177-81.
Full Text: Exclude - no AD outcomes

Goldstein G, Materson BJ, Cushman WC, et al. Treatment of hypertension in the elderly: II. Cognitive and behavioral function. Results of a Department of Veterans Affairs Cooperative Study. Hypertension 1990;15(4):361-9.
Full Text: Exclude - no placebo comparator

Golomb BA, Criqui MH, White H, et al. Conceptual foundations of the UCSD Statin Study: a randomized controlled trial assessing the impact of statins on cognition, behavior, and biochemistry. Arch Intern Med 2004;164(2):153-62.
Full Text: Exclude - no primary data (methods paper)

Gomez-Isla T, Blesa R, Boada M, et al. A randomized, double-blind, placebo controlled-trial of triflusal in mild cognitive impairment: the TRIMCI study. Alzheimer Dis Assoc Disord 2008;22(1):21-9.
Full Text: Exclude - risk factor out of scope

Goodwin JS, Regan M. Cognitive dysfunction associated with naproxen and ibuprofen in the elderly. Arthritis Rheum 1982;25(8):1013-5.
Full Text: Exclude - not applicable population

Goodwin JS, Sanchez CJ, Thomas P, et al. Alcohol intake in a healthy elderly population. Am J Public Health 1987;77(2):173-7.
Full Text: Exclude - risk factor out of scope

Gorelick PB, Brody J, Cohen D, et al. Risk factors for dementia associated with multiple cerebral infarcts. A case-control analysis in predominantly African-American hospital-based patients. Arch Neurol 1993;50(7):714-20.
Full Text: Exclude - selected population

Gow AJ, Johnson W, Pattie A, et al. Mental ability in childhood and cognitive aging. Gerontology 2008;54(3):177-86.
Full Text: Exclude - not longitudinal

Grassi V, Carminati L, Cossi S, et al. [Chronic obstructive lung disease. Systemic manifestations]. Recenti Prog Med 2003;94(5):217-26.
Full Text: Exclude - non-English

Graves AB, Larson EB, Edland SD, et al. Prevalence of

dementia and its subtypes in the Japanese American population of King County, Washington state. The Kame Project. Am J Epidemiol 1996;144(8):760-71.
Full Text: Exclude - not longitudinal

Gray SL, Hanlon JT, Landerman LR, et al. Is antioxidant use protective of cognitive function in the community-dwelling elderly? Am J Geriatr Pharmacother 2003;1(1):3-10.
Full Text: Exclude - SPMSQ single test

Green HJ, Pakenham KI, Headley BC, et al. Quality of life compared during pharmacological treatments and clinical monitoring for non-localized prostate cancer: a randomized controlled trial. BJU Int 2004;93(7):975-9.
Full Text: Exclude - not applicable population

Greendale GA, Kritz-Silverstein D, Seeman T, et al. Higher basal cortisol predicts verbal memory loss in postmenopausal women: Rancho Bernardo Study. J Am Geriatr Soc 2000;48(12):1655-8.
Full Text: Exclude - risk factor out of scope

Grodstein F, Chen J, Willett WC. High-dose antioxidant supplements and cognitive function in community-dwelling elderly women. Am J Clin Nutr 2003;77(4):975-84.
Full Text: Exclude - not longitudinal

Grodstein F, Chen J, Wilson RS, et al. Type 2 diabetes and cognitive function in community-dwelling elderly women. Diabetes Care 2001;24(6):1060-5.
Full Text: Exclude - not longitudinal

Grodstein F, Kang JH, Glynn RJ, et al. A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II. Arch Intern Med 2007;167(20):2184-90.
Full Text: Exclude - not longitudinal

Guo Z, Fratiglioni L, Winblad B, et al. Blood pressure and performance on the Mini-Mental State Examination in the very old. Cross-sectional and longitudinal data from the Kungsholmen Project. Am J Epidemiol 1997;145(12):1106-13.
Full Text: Exclude - dementia @ baseline

Guo Z, Fratiglioni L, Zhu L, et al. Occurrence and progression of dementia in a community population aged 75 years and older: relationship of antihypertensive medication use. Arch Neurol 1999;56(8):991-6.
Full Text: Exclude - <60% of dementia is AD

Gupta R, Solanki RK, Pathak V. Blood pressure is associated with cognitive impairment in young hypertensives. World J Biol Psychiatry 2008;9(1):43-50.
Full Text: Exclude - non-Western country

Gurland BJ, Teresi J, Smith WM, et al. Effects of treatment for isolated systolic hypertension on cognitive status and depression in the elderly. J Am Geriatr Soc 1988;36(11):1015-22.
Full Text: Exclude - covered in existing systematic review

Guskiewicz KM, Marshall SW, Bailes J, et al. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. Neurosurgery 2005;57(4):719-26; discussion 719-26.
Full Text: Exclude - <60% of dementia is AD

Gussekloo J, Heijmans BT, Slagboom PE, et al. Thermolabile methylenetetrahydrofolate reductase gene and the risk of cognitive impairment in those over 85. J Neurol Neurosurg Psychiatry 1999;67(4):535-8.
Full Text: Exclude - observational N<300

Haan MN, Miller JW, Aiello AE, et al. Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging. Am J Clin Nutr 2007;85(2):511-7.
Full Text: Exclude - non-specific dementia in analyses

Hailpern SM, Melamed ML, Cohen HW, et al. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). J Am Soc Nephrol 2007;18(7):2205-13.
Full Text: Exclude - risk factor out of scope

Hajjar I, Catoe H, Sixta S, et al. Cross-sectional and longitudinal association between antihypertensive medications and cognitive impairment in an elderly population. J Gerontol A Biol Sci Med Sci 2005;60(1):67-73.
Full Text: Exclude - dementia @ baseline

Hajjar I, Schumpert J, Hirth V, et al. The impact of the use of statins on the prevalence of dementia and the progression of cognitive impairment. J Gerontol A Biol Sci Med Sci 2002;57(7):M414-8.
Full Text: Exclude - not longitudinal

Hall CB, Lipton RB, Sliwinski M, et al. Cognitive activities delay onset of memory decline in persons who develop dementia. Neurology 2009;73(5):356-61.
Full Text: Exclude - observational N<300

Halyburton AK, Brinkworth GD, Wilson CJ, et al. Low- and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance. Am J Clin Nutr 2007;86(3):580-7.
Full Text: Exclude - AD/CD f/u < 1 yr

Hamidovic A, Kang UJ, de Wit H. Effects of low to moderate acute doses of pramipexole on impulsivity and cognition in healthy volunteers. J Clin Psychopharmacol 2008;28(1):45-51.
Full Text: Excluded - risk factor out of scope

Han C, Jo SA, Seo JA, et al. Adiposity parameters and cognitive function in the elderly: application of "Jolly Fat" hypothesis to cognition. Arch Gerontol Geriatr 2009;49(2):e133-8.
Full Text: Exclude - non-Western country

Han L, Agostini JV, Allore HG. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. J Am Geriatr Soc 2008;56(12):2203-10.
Full Text: Exclude - risk factor out of scope

Hanlon JT, Schmader KE, Landerman LR, et al. Relation of prescription nonsteroidal antiinflammatory drug use to cognitive function among community-dwelling elderly. Ann Epidemiol 1997;7(2):87-94.
Full Text: Exclude - SPMSQ single test

Hanon O, Berrou JP, Negre-Pages L, et al. Effects of hypertension therapy based on eprosartan on systolic arterial blood pressure and cognitive function: primary results of the Observational Study on Cognitive function And Systolic Blood Pressure Reduction open-label study. J Hypertens 2008;26(8):1642-50.
Full Text: Exclude - not longitudinal

Hanon O, Pequignot R, Seux ML, et al. Relationship between antihypertensive drug therapy and cognitive function in elderly hypertensive patients with memory complaints. J Hypertens 2006;24(10):2101-7.
Full Text: Exclude - selected population

Harris SE, Fox H, Wright AF, et al. The brain-derived neurotrophic factor Val66Met polymorphism is associated with age-related change in reasoning skills. Mol Psychiatry 2006;11(5):505-13.
Full Text: Exclude - not applicable population

Hartley DE, Elsabagh S, File SE. Gincosan (a combination of Ginkgo biloba and Panax ginseng): the effects on mood and cognition of 6 and 12 weeks' treatment in post-menopausal women. Nutr Neurosci 2004;7(5-6):325-33.
Full Text: Exclude - not longitudinal

Hassing LB, Grant MD, Hofer SM, et al. Type 2 diabetes mellitus contributes to cognitive decline in old age: a longitudinal population-based study. J Int Neuropsychol Soc 2004;10(4):599-607.
Full Text: Exclude - observational N< 300

Hassing LB, Hofer SM, Nilsson SE, et al. Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. Age Ageing 2004;33(4):355-61.
Full Text: Exclude - observational N<300

Hastings EC, West RL. The relative success of a self-help and a group-based memory training program for older adults. Psychol Aging 2009;24(3):586-94.
Full Text: Exclude - AD/CD f/u < 1 year

Hatch SL, Feinstein L, Link BG, et al. The continuing benefits of education: adult education and midlife cognitive ability in the British 1946 birth cohort. J Gerontol B Psychol Sci Soc Sci 2007;62(6):S404-14.
Full Text: Exclude - not longitudinal

Hayashi T, Nomura H, Osawa M, et al. Nitric oxide metabolites are associated with survival in older patients. J Am Geriatr Soc 2007;55(9):1398-403.
Full Text: Exclude - risk factor out of scope

Hayward L, Mant A, Eyland A, et al. Sleep disordered breathing and cognitive function in a retirement village population. Age Ageing 1992;21(2):121-8.
Full Text: Exclude - observational N<300

Heckbert SR, Longstreth WT, Jr., Psaty BM, et al. The association of antihypertensive agents with MRI white matter findings and with Modified Mini-Mental State Examination in older adults. J Am Geriatr Soc 1997;45(12):1423-33.
Full Text: Exclude - not longitudinal

Heitner J, Dickson D. Diabetics do not have increased Alzheimer-type pathology compared with age-matched control subjects. A retrospective postmortem immunocytochemical and histofluorescent study. Neurology 1997;49(5):1306-11.
Full Text: Exclude - outcomes unacceptably assessed

Helbecque N, Codron V, Cottel D, et al. An apolipoprotein A-I gene promoter polymorphism associated with cognitive decline, but not with Alzheimer's disease. Dement Geriatr Cogn Disord 2008;25(2):97-102.
Full Text: Exclude - not applicable population

Helmer C, Peuchant E, Letenneur L, et al. Association between antioxidant nutritional indicators and the incidence of dementia: results from the PAQUID prospective cohort study. Eur J Clin Nutr 2003;57(12):1555-61.
Full Text: Exclude - <60% of dementia is AD

Henderson AS, Jorm AF, Christensen H, et al. Aspirin, anti-inflammatory drugs and risk of dementia. Int J Geriatr Psychiatry 1997;12(9):926-30.
Full Text: Exclude - <60% of dementia is AD

Henderson AS, Jorm AF, Mackinnon A, et al. A survey of dementia in the Canberra population: experience with ICD-10 and DSM-III-R criteria. Psychol Med 1994;24(2):473-82.
Full Text: Exclude - risk factor out of scope

Henderson VW, Guthrie JR, Dennerstein L. Serum lipids and memory in a population based cohort of middle age women. J Neurol Neurosurg Psychiatry 2003;74(11):1530-5.
Full Text: Exclude - <60% of dementia is AD

Henderson VW, Guthrie JR, Dudley EC, et al. Estrogen exposures and memory at midlife: a population-based study of women. Neurology 2003;60(8):1369-71.
Full Text: Exclude - <60% of dementia is AD

Hendrie HC, Hall KS, Ogunniyi A, et al. Alzheimer's disease, genes, and environment: the value of international studies. Can J Psychiatry 2004;49(2):92-9.
Full Text: Exclude - not longitudinal

Hengstermann S, Laemmler G, Hanemann A, et al. Total serum homocysteine levels do not identify cognitive dysfunction in multimorbid elderly patients. J Nutr Health Aging 2008;12(6):411-6.
Full Text: Exclude - not longitudinal

Hengstermann S, Laemmler G, Hanemann A, et al. Total serum homocysteine levels do not identify cognitive dysfunction in multimorbid elderly patients. J Nutr Health Aging 2009;13(2):121-6.
Full Text: Exclude - not applicable population

Hertzog C, Schaie KW, Gribbin K. Cardiovascular disease and changes in intellectual functioning from middle to old age. J Gerontol 1978;33(6):872-83.
Full Text: Exclude - observational N<300

Hestad KA, Engedal K. Antihypertensive medication is associated with less cognitive impairment in the very old with apolipoprotein-E epsilon4 allele. Drugs Aging 2006;23(9):723-31.
Full Text: Exclude - not longitudinal

Heude B, Ducimetiere P, Berr C. Cognitive decline and fatty acid composition of erythrocyte membranes--The EVA Study. Am J Clin Nutr 2003;77(4):803-8.
Full Text: Exclude - observational N<300

Heun R, Kolsch H, Jessen F. Risk factors and early signs of Alzheimer's disease in a family study sample. Risk of AD. Eur Arch Psychiatry Clin Neurosci 2006;256(1):28-36.
Full Text: Exclude - not applicable population

Heyer EJ, Wilson DA, Sahlein DH, et al. APOE-epsilon4 predisposes to cognitive dysfunction following uncomplicated carotid endarterectomy. Neurology 2005;65(11):1759-63.
Full Text: Exclude - selected population

Hillen T, Lun A, Reischies FM, et al. DHEA-S plasma levels and incidence of Alzheimer's disease. Biol Psychiatry 2000;47(2):161-3.
Full Text: Exclude - observational N<300

Himanen L, Portin R, Isoniemi H, et al. Longitudinal cognitive changes in traumatic brain injury: a 30-year follow-up study. Neurology 2006;66(2):187-92.
Full Text: Exclude - observational N<300

Ho SC, Chan AS, Ho YP, et al. Effects of soy isoflavone supplementation on cognitive function in Chinese postmenopausal women: a double-blind, randomized, controlled trial. Menopause 2007;14(3 Pt 1):489-99.
Full Text: Exclude - AD/CD f/u < 1 yr

Hofer SM, Christensen H, Mackinnon AJ, et al. Change in cognitive functioning associated with apoE genotype in a community sample of older adults. Psychol Aging 2002;17(2):194-208.
Full Text: Exclude - observational N<300

Hoffman LB, Schmeidler J, Lesser GT, et al. Less Alzheimer disease neuropathology in medicated hypertensive than nonhypertensive persons. Neurology 2009;72(20):1720-6.
Full Text: Exclude - not applicable population

Hofman A, Ott A, Breteler MM, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study.[see comment]. Lancet 1997;349(9046):151-4.
Full Text: Exclude - risk factor out of scope

Hogervorst E, Sadjimim T, Yesufu A, et al. High tofu intake is associated with worse memory in elderly Indonesian men and women. Dement Geriatr Cogn Disord 2008;26(1):50-7.
Full Text: Exclude - non-Western country

Hohaus L. Remembering to age successfully: evaluation of a successful aging approach to memory enhancement. Int Psychogeriatr 2007;19(1):137-50.
Full Text: Exclude - AD/CD f/u < 1 yr

Honig LS, Tang MX, Albert S, et al. Stroke and the risk of Alzheimer disease. Arch Neurol 2003;60(12):1707-12.
Full Text: Exclude - risk factor out of scope

Houlihan LM, Harris SE, Luciano M, et al. Replication study of candidate genes for cognitive abilities: the Lothian Birth Cohort 1936. Genes Brain Behav 2009;8(2):238-47.
Full Text: Exclude - not longitudinal

Howe MN, Price IR. Effects of transdermal nicotine on learning, memory, verbal fluency, concentration, and general health in a healthy sample at risk for dementia. Int Psychogeriatr 2001;13(4):465-75.
Full Text: Exclude - AD/CD f/u < 1 yr

Howe MN, Price IR. Effects of transdermal nicotine on learning, memory, verbal fluency, concentration, and general health in a healthy sample at risk for dementia. Int Psychogeriatr 2001;13(4):465-75.
Full Text: Exclude - AD/CD f/u < 1 yr

Hsu HC. Does social participation by the elderly reduce mortality and cognitive impairment? Aging Ment Health 2007;11(6):699-707.
Full Text: Exclude - SPMSQ single test

Hu L, Yue Y, Zuo PP, et al. Evaluation of neuroprotective effects of long-term low dose hormone replacement therapy on postmenopausal women brain hippocampus using magnetic resonance scanner. Chin Med Sci J 2006;21(4):214-8.
Full Text: Exclude - non-Western country

Huang CQ, Dong BR, Zhang YL, et al. Association of cognitive impairment with smoking, alcohol consumption, tea consumption, and exercise among Chinese nonagenarians/centenarians. Cogn Behav Neurol 2009;22(3):190-6.
Full Text: Exclude - non-Western country

Hughes TF, Andel R, Small BJ, et al. The association between social resources and cognitive change in older adults: evidence from the Charlotte County Healthy Aging Study. J Gerontol B Psychol Sci Soc Sci 2008;63(4):P241-P244.
Full Text: Exclude - observational N<300

Huijbregts PP, Feskens EJ, Rasanen L, et al. Dietary patterns and cognitive function in elderly men in Finland, Italy and The Netherlands. Eur J Clin Nutr 1998;52(11):826-31.
Full Text: Exclude - not longitudinal

Hultsch DF, Hammer M, Small BJ. Age differences in cognitive performance in later life: relationships to self-reported health and activity life style. J Gerontol 1993;48(1):P1-11.
Full Text: Exclude - not longitudinal

Hultsch DF, Hertzog C, Small BJ, et al. Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging? Psychol Aging 1999;14(2):245-63.
Full Text: Exclude - observational N<300

Incalzi RA, Corsonello A, Trojano L, et al. Cognitive training is ineffective in hypoxemic COPD: a six-month randomized controlled trial. Rejuvenation Res 2008;11(1):239-50.
Full Text: Exclude - selected population

Israel L, Melac M, Milinkevitch D, et al. Drug therapy and memory training programs: a double-blind randomized trial of general practice patients with age-associated memory impairment. Int Psychogeriatr 1994;6(2):155-70.
Full Text: Exclude - AD/CD f/u < 1 yr

Jack CR, Jr., Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 1999;52(7):1397-403.
Full Text: Exclude - risk factor out of scope

Jagger C, Matthews R, Matthews F, et al. The burden of diseases on disability-free life expectancy in later life. J Gerontol A Biol Sci Med Sci 2007;62(4):408-14.
Full Text: Exclude - dementia @ baseline

Jama JW, Launer LJ, Witteman JC, et al. Dietary antioxidants and cognitive function in a population-based sample of older persons. The Rotterdam Study. Am J Epidemiol 1996;144(3):275-80.
Full Text: Exclude - not longitudinal

Janke MC, Payne LL, Van Puymbroeck M. The role of informal and formal leisure activities in the disablement process. Int J Aging Hum Dev 2008;67(3):231-57.
Full Text: Exclude - not relevant outcomes

Jick H, Zornberg GL, Jick S, et al. Statins and the risk of dementia. Lancet 2000;356(9242):1627-31.
Full Text: Exclude - outcome non-specific AD

Johnson EJ, McDonald K, Caldarella SM, et al. Cognitive findings of an exploratory trial of docosahexaenoic acid and lutein supplementation in older women. Nutr Neurosci 2008;11(2):75-83.
Full Text: Exclude - AD/CD f/u < 1 yr

Johnson KC, Margolis KL, Espeland MA, et al. A prospective study of the effect of hypertension and baseline blood pressure on cognitive decline and dementia in postmenopausal women: the Women's Health Initiative Memory Study. J Am Geriatr Soc 2008;56(8):1449-58.
Full Text: Exclude - <60% of dementia is AD

Jonsson L, Gerth W, Fastbom J. The potential economic consequences of cognitive improvement with losartan. Blood Press 2002;11(1):46-52.
Full Text: Exclude - outcomes not AD/CD

Jorissen BL, Brouns F, Van Boxtel MP, et al. The influence of soy-derived phosphatidylserine on cognition in age-associated memory impairment. Nutr Neurosci 2001;4(2):121-34.
Full Text: Exclude - AD/CD f/u < 1 yr

Kadoi Y, Goto F. Factors associated with postoperative cognitive dysfunction in patients undergoing cardiac surgery. Surg Today 2006;36(12):1053-7.
Full Text: Exclude - selected population

Kagan A, Popper JS, Rhoads GG. Factors related to stroke incidence in Hawaii Japanese men. The Honolulu Heart Study. Stroke 1980;11(1):14-21.
Full Text: Exclude - not applicable population

Kahonen MH, Tilvis RS, Jolkkonen J, et al. Predictors and clinical significance of declining plasma dehydroepiandrosterone sulfate in old age. Aging (Milano) 2000;12(4):308-14.
Full Text: Exclude - observational N<300

Kahonen-Vare M, Brunni-Hakala S, Lindroos M, et al. Left ventricular hypertrophy and blood pressure as predictors of cognitive decline in old age. Aging Clin Exp Res 2004;16(2):147-52.
Full Text: Exclude - observational N<300

Kalaydjian A, Zandi PP, Swartz KL, et al. How migraines impact cognitive function: findings from the Baltimore ECA. Neurology 2007;68(17):1417-24.
Full Text: Exclude - risk factor out of scope

Kalmijn S, Feskens EJ, Launer LJ, et al. Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. Diabetologia 1995;38(9):1096-102.
Full Text: Exclude - not longitudinal

Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. Arterioscler Thromb Vasc Biol 2000;20(10):2255-60.
Full Text: Exclude - RF not assessed adequately

Kalmijn S, Launer LJ, Stolk RP, et al. A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. J Clin Endocrinol Metab 1998;83(10):3487-92.
Full Text: Exclude - observational N<300

Kalmijn S, van Boxtel MP, Ocke M, et al. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology 2004;62(2):275-80.
Full Text: Exclude - not longitudinal

Kanoni S, Dedoussis GV. Design and descriptive characteristics of the GHRAS: the Greek Health Randomized Aging Study. Med Sci Monit 2008;14(4):CR204-12.
Full Text: Exclude - Outcomes not AD/CD

Kanowski S, Hoerr R. Ginkgo biloba extract EGb 761 in dementia: intent-to-treat analyses of a 24-week, multi-center, double-blind, placebo-controlled, randomized trial. Pharmacopsychiatry 2003;36(6):297-303.
Full Text: Exclude - dementia @ baseline

Karlamangla AS, Singer BH, Chodosh J, et al. Urinary cortisol excretion as a predictor of incident cognitive impairment. Neurobiol Aging 2005;26 Suppl 1:80-4.
Full Text: Exclude - risk factor out of scope

Karlamangla AS, Singer BH, Reuben DB, et al. Increases in serum non-high-density lipoprotein cholesterol may be beneficial in some high-functioning older adults: MacArthur studies of successful aging. J Am Geriatr Soc 2004;52(4):487-94.
Full Text: Exclude - observational N<300

Katsuya T, Baba S, Ishikawa K, et al. Epsilon 4 allele of apolipoprotein E gene associates with lower blood pressure in young Japanese subjects: the Suita Study. J Hypertens 2002;20(10):2017-21.
Full Text: Exclude - Outcomes not AD/CD

Kearney-Schwartz A, Rossignol P, Bracard S, et al. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. Stroke 2009;40(4):1229-36.
Full Text: Exclude - AD/CD f/u < 1 yr

Keenan PA, Jacobson MW, Soleymani RM, et al. The effect on memory of chronic prednisone treatment in patients with systemic disease. Neurology 1996;47(6):1396-402.
Full Text: Exclude - AD/CD f/u < 1 yr

Kenny AM, Bellantonio S, Gruman CA, et al. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2002;57(5):M321-5.
Full Text: Exclude - RCT N<50

Kharrazi H, Vaisi-Raygani A, Rahimi Z, et al. Association between enzymatic and non-enzymatic antioxidant defense mechanism with apolipoprotein E genotypes in Alzheimer disease. Clin Biochem 2008;41(12):932-6.
Full Text: Exclude - dementia @ baseline

Kilander L, Nyman H, Boberg M, et al. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. Hypertension 1998;31(3):780-6.
Full Text: Exclude - not longitudinal

Kilander L, Nyman H, Boberg M, et al. Cognitive function, vascular risk factors and education. A cross-sectional study based on a cohort of 70-year-old men. J Intern Med 1997;242(4):313-21.
Full Text: Exclude - not longitudinal

Kim JM, Stewart R, Kim SW, et al. Changes in folate, vitamin B12 and homocysteine associated with incident dementia. J Neurol Neurosurg Psychiatry 2008;79(8):864-8.
Full Text: Exclude - dementia @ baseline

Kim JM, Stewart R, Prince M, et al. Dental health, nutritional status and recent-onset dementia in a Korean community population. Int J Geriatr Psychiatry 2007;22(9):850-5.
Full Text: Exclude - risk factor out of scope

King R, Travers C, O'Neill S, et al. The influence of postmenopausal hormone replacement therapy on cognitive functioning: results from an observational study. J Br Menopause Soc 2004;10(3):103-7.
Full Text: Exclude - not longitudinal

Kinsella GJ, Mullaly E, Rand E, et al. Early intervention for mild cognitive impairment: a randomised controlled trial. J Neurol Neurosurg Psychiatry 2009;80(7):730-6.
Full Text: Exclude - AD/CD f/u < 1 yr

Kivipelto M, Annerbo S, Hultdin J, et al. Homocysteine and holo-transcobalamin and the risk of dementia and Alzheimers disease: a prospective study. Eur J Neurol 2009;16(7):808-13.
Full Text: Exclude - observational N<300

Kivipelto M, Helkala EL, Hanninen T, et al. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology 2001;56(12):1683-9.
Full Text: Exclude - outcomes assessed inadequately

Klonoff H, Clark C, Kavanagh-Gray D, et al. Two-year follow-up study of coronary bypass surgery. Psychologic status, employment status, and quality of life. J Thorac Cardiovasc Surg 1989;97(1):78-85.
Full Text: Exclude - not applicable population

Knecht S, Wersching H, Lohmann H, et al. How much does hypertension affect cognition?: explained variance in cross-sectional analysis of non-demented community-dwelling individuals in the SEARCH study. J Neurol Sci 2009;283(1-2):149-52.
Full Text: Exclude - not longitudinal

Knight RG, McMahon J, Skeaff CM, et al. Reliable Change Index scores for persons over the age of 65 tested on alternate forms of the Rey AVLT. Arch Clin Neuropsychol 2007;22(4):513-8.
Full Text: Exclude - risk factor out of scope

Knopman DS. Hypertension and late-life dementia: A real link? Neurology 2009;72(20):1716-7.
Full Text: Exclude - no data, editorial

Komulainen P, Lakka TA, Kivipelto M, et al. Metabolic syndrome and cognitive function: a population-based follow-up study in elderly women. Dement Geriatr Cogn Disord 2007;23(1):29-34.
Full Text: Exclude - observational N<300

Koontz J, Baskys A. Effects of galantamine on working memory and global functioning in patients with mild cognitive impairment: a double-blind placebo-controlled study. Am J Alzheimers Dis Other Demen 2005;20(5):295-302.
Full Text: Exclude - RCT N<50

Korf ES, White LR, Scheltens P, et al. Brain aging in very old men with type 2 diabetes: the Honolulu-Asia Aging Study. Diabetes Care 2006;29(10):2268-74.
Full Text: Exclude - risk factor out of scope

Korten AE, Henderson AS, Christensen H, et al. A prospective study of cognitive function in the elderly. Psychol Med 1997;27(4):919-30.
Full Text: Exclude - risk factor out of scope

Kostis JB, Rosen R, Wilson A. Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. J Clin Pharmacol 1994;34(10):989-96.
Full Text: Exclude - RCT N<50

Kotani S, Sakaguchi E, Warashina S, et al. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. Neurosci Res 2006;56(2):159-64.
Full Text: Exclude - dementia @ baseline

Kreijkamp-Kaspers S, Kok L, Grobbee DE, et al. Dietary phytoestrogen intake and cognitive function in older women. J Gerontol A Biol Sci Med Sci 2007;62(5):556-62.
Full Text: Exclude - not longitudinal

Kritz-Silverstein D, Von Muhlen D, Barrett-Connor E, et al. Isoflavones and cognitive function in older women: the SOy and Postmenopausal Health In Aging (SOPHIA) Study. Menopause 2003;10(3):196-202.
Full Text: Exclude - AD/CD f/u < 1 yr

Kuningas M, de Rijk RH, Westendorp RG, et al. Mental performance in old age dependent on cortisol and genetic variance in the mineralocorticoid and glucocorticoid receptors. Neuropsychopharmacology 2007;32(6):1295-301.
Full Text: Exclude - risk factor out of scope

Kurinami H, Sato N, Shinohara M, et al. Prevention of amyloid beta-induced memory impairment by fluvastatin, associated with the decrease in amyloid beta accumulation and oxidative stress in amyloid beta injection mouse model. Int J Mol Med 2008;21(5):531-7.
Full Text: Exclude - not applicable population

Kurt M, Bekci B, Karakas S. Hormone replacement therapy and cognitive function in postmenopausal women. Maturitas 2006;53(1):39-48.
Full Text: Exclude - non-Western country

Kurtz MM, Gerraty RT. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. Neuropsychology 2009;23(5):551-62.
Full Text: Exclude - not applicable population

Kuusisto J, Koivisto K, Mykkanen L, et al. Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study. BMJ 1997;315(7115):1045-9.
Full Text: Exclude - not longitudinal

La Rue A, Koehler KM, Wayne SJ, et al. Nutritional status and cognitive functioning in a normally aging sample: a 6-y reassessment. Am J Clin Nutr 1997;65(1):20-9.
Full Text: Exclude - observational N<300

Laitala VS, Kaprio J, Koskenvuo M, et al. Coffee drinking in middle age is not associated with cognitive performance in old age. Am J Clin Nutr 2009;90(3):640-6.
Full Text: Exclude - outcomes inadequately assessed

Landi F, Cesari M, Onder G, et al. Non-steroidal anti-inflammatory drug (NSAID) use and Alzheimer disease in community-dwelling elderly patients. Am J Geriatr Psychiatry 2003;11(2):179-85.
Full Text: Exclude - dementia @ baseline

Landi F, Russo A, Liperoti R, et al. Anticholinergic drugs and physical function among frail elderly population. Clin Pharmacol Ther 2007;81(2):235-41.
Full Text: Exclude - risk factor out of scope

Lane R, He Y, Morris C, et al. BuChE-K and APOE epsilon4 allele frequencies in Lewy body dementias, and influence of genotype and hyperhomocysteinemia on cognitive decline. Mov Disord 2009;24(3):392-400.
Full Text: Exclude - selected population

Lang IA, Llewellyn DJ, Langa KM, et al. Neighborhood deprivation, individual socioeconomic status, and cognitive function in older people: analyses from the English Longitudinal Study of Ageing. J Am Geriatr Soc 2008;56(2):191-8.
Full Text: Exclude - not longitudinal

Langbaum JB, Rebok GW, Bandeen-Roche K, et al.

Predicting memory training response patterns: results from ACTIVE. J Gerontol B Psychol Sci Soc Sci 2009;64(1):14-23.
Full Text: Exclude - secondary analysis of data

Lasser NL, Nash J, Lasser VI, et al. Effects of antihypertensive therapy on blood pressure control, cognition, and reactivity. A placebo-controlled comparison of prazosin, propranolol, and hydrochlorothiazide. Am J Med 1989;86(1B):98-103.
Full Text: Exclude - AD/CD f/u < 1 yr

Launer LJ, Dinkgreve MA, Jonker C, et al. Are age and education independent correlates of the Mini-Mental State Exam performance of community-dwelling elderly? J Gerontol 1993;48(6):P271-7.
Full Text: Exclude - not longitudinal

Launer LJ, Masaki K, Petrovitch H, et al. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. JAMA 1995;274(23):1846-51.
Full Text: Exclude - not longitudinal

Laurin D, Verreault R, Lindsay J, et al. Omega-3 fatty acids and risk of cognitive impairment and dementia. J Alzheimers Dis 2003;5(4):315-22.
Full Text: Exclude - observational N<300

Lechevallier-Michel N, Molimard M, Dartigues JF, et al. Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. Br J Clin Pharmacol 2005;59(2):143-51.
Full Text: Exclude - not longitudinal

Lee BK, Glass TA, McAtee MJ, et al. Associations of salivary cortisol with cognitive function in the Baltimore memory study. Arch Gen Psychiatry 2007;64(7):810-8.
Full Text: Exclude - risk factor out of scope

Lee H, Wintermark M, Gean AD, et al. Focal lesions in acute mild traumatic brain injury and neurocognitive outcome: CT versus 3T MRI. J Neurotrauma 2008;25(9):1049-56.
Full Text: Exclude - risk factor out of scope

Lee JY, Chang SM, Jang HS, et al. Illiteracy and the incidence of Alzheimer's disease in the Yonchon County survey, Korea. Int Psychogeriatr 2008;20(5):976-85.
Full Text: Exclude - risk factor out of scope

Lee L, Kang SA, Lee HO, et al. Relationships between dietary intake and cognitive function level in Korean elderly people. Public Health 2001;115(2):133-8.
Full Text: Exclude - non-Western country

Lee LK, Shahar S, Rajab N. Serum folate concentration, cognitive impairment, and DNA damage among elderly individuals in Malaysia. Nutr Res 2009;29(5):327-34.
Full Text: Exclude - non-Western country

Leibovici D, Ritchie K, Ledesert B, et al. The effects of wine and tobacco consumption on cognitive performance in the elderly: a longitudinal study of relative risk. Int J Epidemiol 1999;28(1):77-81.
Full Text: Exclude - observational N<300

Leibson CL, Rocca WA, Hanson VA, et al. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. Am J Epidemiol 1997;145(4):301-8.
Full Text: Exclude - outcomes unacceptably assessed

Lessov-Schlaggar CN, Reed T, Swan GE, et al. Association of sex steroid hormones with brain morphology and cognition in healthy elderly men. Neurology 2005;65(10):1591-6.
Full Text: Exclude - not longitudinal

Letenneur L, Dartigues JF, Commenges D, et al. Tobacco consumption and cognitive impairment in elderly people. A population-based study. Ann Epidemiol 1994;4(6):449-54.
Full Text: Exclude - not longitudinal

Levine B, Stuss DT, Winocur G, et al. Cognitive rehabilitation in the elderly: effects on strategic behavior in relation to goal management. J Int Neuropsychol Soc 2007;13(1):143-52.
Full Text: Exclude - RCT N<50

Li G, Cherrier MM, Tsuang DW, et al. Salivary cortisol and memory function in human aging. Neurobiol Aging 2006;27(11):1705-14.
Full Text: Exclude - risk factor out of scope

Llewellyn DJ, Lang IA, Langa KM, et al. Exposure to secondhand smoke and cognitive impairment in non-smokers: national cross sectional study with cotinine measurement. BMJ 2009;338:b462.
Full Text: Exclude - risk factor out of scope

Llewellyn DJ, Lang IA, Xie J, et al. Framingham Stroke Risk Profile and poor cognitive function: a population-based study. BMC Neurol 2008;8:12.
Full Text: Exclude - not longitudinal

Louis WJ, Mander AG, Dawson M, et al. Use of computerized neuropsychological tests (CANTAB) to assess cognitive effects of antihypertensive drugs in the elderly. Cambridge Neuropsychological Test Automated Battery. J Hypertens 1999;17(12 Pt 2):1813-9.
Full Text: Exclude - AD/CD f/u < 1 yr

Luchsinger JA, Tang MX, Mayeux R. Glycemic load and risk of Alzheimer's disease. J Nutr Health Aging 2007;11(3):238-41.
Full Text: Exclude - risk factor out of scope

Luchsinger JA, Tang MX, Miller J, et al. Higher folate intake is related to lower risk of Alzheimer's disease in the elderly. J Nutr Health Aging 2008;12(9):648-50.
Full Text: Exclude - summary duplicate of study outcomes

Luchsinger JA, Tang MX, Shea S, et al. Hyperinsulinemia

and risk of Alzheimer disease. Neurology 2004;63(7):1187-92.
Full Text: Exclude - risk factor out of scope

Luchsinger JA, Tang MX, Siddiqui M, et al. Alcohol intake and risk of dementia. J Am Geriatr Soc 2004;52(4):540-6.
Full Text: Exclude - risk factor out of acope

Luciano M, Gow AJ, Harris SE, et al. Cognitive ability at age 11 and 70 years, information processing speed, and APOE variation: the Lothian Birth Cohort 1936 study. Psychol Aging 2009;24(1):129-38.
Full Text: Exclude - not longitudinal

Luciano M, Gow AJ, Taylor MD, et al. Apolipoprotein E is not related to memory abilities at 70 years of age. Behav Genet 2009;39(1):6-14.
Full Text: Exclude - outcomes unacceptably assessed

Lupien S, Lecours AR, Lussier I, et al. Basal cortisol levels and cognitive deficits in human aging. J Neurosci 1994;14(5 Pt 1):2893-903.
Full Text: Exclude - risk factor out of scope

Lupien SJ, Schwartz G, Ng YK, et al. The Douglas Hospital Longitudinal Study of Normal and Pathological Aging: summary of findings. J Psychiatry Neurosci 2005;30(5):328-34.
Full Text: Exclude - risk factor out of scope

Luukinen H, Viramo P, Koski K, et al. Head injuries and cognitive decline among older adults: a population-based study. Neurology 1999;52(3):557-62.
Full Text: Exclude - not longitudinal

MacKenzie SM, Dewar D, Stewart W, et al. The transcription of steroidogenic genes in the human cerebellum and hippocampus: a comparative survey of normal and Alzheimer's tissue. J Endocrinol 2008;196(1):123-30.
Full Text: Exclude - not applicable population

MacLullich AM, Deary IJ, Starr JM, et al. Plasma cortisol levels, brain volumes and cognition in healthy elderly men. Psychoneuroendocrinology 2005;30(5):505-15.
Full Text: Exclude - risk factor out of scope

Madden DJ, Blumenthal JA, Allen PA, et al. Improving aerobic capacity in healthy older adults does not necessarily lead to improved cognitive performance. Psychol Aging 1989;4(3):307-20.
Full Text: Exclude - AD/CD f/u < 1 yr

Mainous AG, 3rd, Eschenbach SL, Wells BJ, et al. Cholesterol, transferrin saturation, and the development of dementia and Alzheimer's disease: results from an 18-year population-based cohort. Fam Med 2005;37(1):36-42.
Full Text: Exclude - outcomes unacceptably assessed

Maioli F, Coveri M, Pagni P, et al. Conversion of mild cognitive impairment to dementia in elderly subjects: a preliminary study in a memory and cognitive disorder unit. Arch Gerontol Geriatr 2007;44 Suppl 1:233-41.
Full Text: Exclude - observational N<300

Mak Z, Kim JM, Stewart R. Leg length, cognitive impairment and cognitive decline in an African-Caribbean population. Int J Geriatr Psychiatry 2006;21(3):266-72.
Full Text: Exclude - observational N<300

Malaguarnera M, Ferri R, Bella R, et al. Homocysteine, vitamin B12 and folate in vascular dementia and in Alzheimer disease. Clin Chem Lab Med 2004;42(9):1032-5.
Full Text: Exclude - dementia @ baseline

Mandal B, Roe B. Job loss, retirement and the mental health of older Americans. J Ment Health Policy Econ 2008;11(4):167-76.
Full Text: Exclude - outcomes not acceptably assessed

Manly JJ, Bell-McGinty S, Tang MX, et al. Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. Arch Neurol 2005;62(11):1739-46.
Full Text: Exclude - risk factor out of scope

Manly JJ, Touradji P, Tang MX, et al. Literacy and memory decline among ethnically diverse elders. J Clin Exp Neuropsychol 2003;25(5):680-90.
Full Text: Exclude - observational N<300

Manzato E, Roselli della Rovere G, Zambon S, et al. Cognitive functions are not affected by dietary fatty acids in elderly subjects in the Pro.V.A. study population. Aging Clin Exp Res 2003;15(1):83-6.
Full Text: Exclude - observational N<300

Marcellini F, Giuli C, Papa R, et al. Zinc status, psychological and nutritional assessment in old people recruited in five European countries: Zincage study. Biogerontology 2006;7(5-6):339-45.
Full Text: Exclude - not longitudinal

Marcopulos B, McLain C. Are our norms "normal"? A 4-year follow-up study of a biracial sample of rural elders with low education. Clin Neuropsychol 2003;17(1):19-33.
Full Text: Exclude - observational N<300

Marder K. Vitamin E and donepezil for the treatment of mild cognitive impairment. Curr Neurol Neurosci Rep 2005;5(5):337-8.
Full Text: Exclude - no primary data

Mariani E, Monastero R, Ercolani S, et al. Vascular risk factors in mild cognitive impairment subtypes. Findings from the ReGAl project. Dement Geriatr Cogn Disord 2007;24(6):448-56.
Full Text: Exclude - observational N<300

Marin DB, Breuer B, Marin ML, et al. The relationship between apolipoprotein E, dementia, and vascular illness. Atherosclerosis 1998;140(1):173-80.
Full Text: Exclude - dementia @ baseline

Marklund N, Peltonen M, Nilsson TK, et al. Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. J Intern Med 2004;256(1):15-21.
Full Text: Exclude - risk factor out of scope

Martin CK, Anton SD, Han H, et al. Examination of cognitive function during six months of calorie restriction: results of a randomized controlled trial. Rejuvenation Res 2007;10(2):179-90.
Full Text: Exclude - AD/CD f/u < 1 yr

Maruyama M, Matsui T, Tanji H, et al. Cerebrospinal fluid tau protein and periventricular white matter lesions in patients with mild cognitive impairment: implications for 2 major pathways. Arch Neurol 2004;61(5):716-20.
Full Text: Exclude - risk factor out of scope

Marx BP, Brailey K, Proctor SP, et al. Association of time since deployment, combat intensity, and posttraumatic stress symptoms with neuropsychological outcomes following Iraq war deployment. Arch Gen Psychiatry 2009;66(9):996-1004.
Full Text: Exclude - risk factor out of scope

Mas E, Dupuy AM, Artero S, et al. Functional Vitamin E deficiency in ApoE4 patients with Alzheimer's disease. Dement Geriatr Cogn Disord 2006;21(3):198-204.
Full Text: Exclude - dementia @ baseline

Masley S, Roetzheim R, Gualtieri T. Aerobic exercise enhances cognitive flexibility. J Clin Psychol Med Settings 2009;16(2):186-93.
Full Text: Exclude - <80% >= 50 yo

Mathieu A, Mazza S, Decary A, et al. Effects of obstructive sleep apnea on cognitive function: a comparison between younger and older OSAS patients. Sleep Med 2008;9(2):112-20.
Full Text: Exclude - observational N<300

Mauri M, Sinforiani E, Bono G, et al. Interaction between Apolipoprotein epsilon 4 and traumatic brain injury in patients with Alzheimer's disease and Mild Cognitive Impairment. Funct Neurol 2006;21(4):223-8.
Full Text: Exclude - observational N<300

May FE, Moore MT, Stewart RB, et al. Lack of association of nonsteroidal anti-inflammatory drug use and cognitive decline in the elderly. Gerontology 1992;38(5):275-9.
Full Text: Exclude - not longitudinal

Mazza M, Capuano A, Bria P, et al. Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. Eur J Neurol 2006;13(9):981-5.
Full Text: Exclude - dementia @ baseline

McCaddon A, Hudson P, Davies G, et al. Homocysteine and cognitive decline in healthy elderly. Dement Geriatr Cogn Disord 2001;12(5):309-13.
Full Text: Exclude - observational N<300

McEntee WJ, Crook TH, Jenkyn LR, et al. Treatment of age-associated memory impairment with guanfacine. Psychopharmacol Bull 1991;27(1):41-6.
Full Text: Exclude - AD/CD f/u < 1 yr

McGeer PL, McGeer EG. The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. Brain Research - Brain Research Reviews 1995;21(2):195-218.
Full Text: Exclude - not longitudinal

McGue M, Christensen K. Social activity and healthy aging: a study of aging Danish twins. Twin Res Hum Genet 2007;10(2):255-65.
Full Text: Exclude - dementia @ baseline

McGuire LC, Ajani UA, Ford ES. Cognitive functioning in late life: the impact of moderate alcohol consumption. Ann Epidemiol 2007;17(2):93-9.
Full Text: Exclude - not longitudinal

McGurn B, Deary IJ, Starr JM. Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia. Neurology 2008;71(14):1051-6.
Full Text: Exclude - not longitudinal

McIlroy SP, Dynan KB, Lawson JT, et al. Moderately elevated plasma homocysteine, methylenetetrahydrofolate reductase genotype, and risk for stroke, vascular dementia, and Alzheimer disease in Northern Ireland. Stroke 2002;33(10):2351-6.
Full Text: Exclude - dementia @ baseline

McLaurin EY, Holliday SL, Williams P, et al. Predictors of cognitive dysfunction in patients with systemic lupus erythematosus. Neurology 2005;64(2):297-303.
Full Text: Exclude - not applicable population

McLay RN, Maki PM, Lyketsos CG. Nulliparity and late menopause are associated with decreased cognitive decline. J Neuropsychiatry Clin Neurosci 2003;15(2):161-7.
Full Text: Exclude - risk factor out of scope

McMorris T, Mielcarz G, Harris RC, et al. Creatine supplementation and cognitive performance in elderly individuals. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2007;14(5):517-28.
Full Text: Exclude - risk factor out of scope

Meinert CL, McCaffrey LD, Breitner JC. Alzheimer's Disease Anti-inflammatory Prevention Trial: design, methods, and baseline results. Alzheimers Dement 2009;5(2):93-104.
Full Text: Exclude - risk factor out of scope

Mendelsohn AB, Belle SH, Stoehr GP, et al. Use of antioxidant supplements and its association with cognitive function in a rural elderly cohort: the MoVIES Project. Monongahela Valley Independent Elders Survey. Am J Epidemiol 1998;148(1):38-44.

Full Text: Exclude - not longitudinal

Menec VH. The relation between everyday activities and successful aging: a 6-year longitudinal study. Journals of Gerontology Series B-Psychological Sciences & Social Sciences 2003;58(2):S74-82.
Full Text: Exclude - outcomes unacceptably assessed

Meyer JS, Rauch G, Rauch RA, et al. Risk factors for cerebral hypoperfusion, mild cognitive impairment, and dementia. Neurobiol Aging 2000;21(2):161-9.
Full Text: Exclude - observational N<300

Meyer JS, Rauch GM, Crawford K, et al. Risk factors accelerating cerebral degenerative changes, cognitive decline and dementia. Int J Geriatr Psychiatry 1999;14(12):1050-61.
Full Text: Exclude - observational N<300

Meyer JS, Rauch GM, Rauch RA, et al. Cardiovascular and other risk factors for Alzheimer's disease and vascular dementia. Ann N Y Acad Sci 2000;903:411-23.
Full Text: Exclude - observational N<300

Middleton LE, Kirkland SA, Maxwell CJ, et al. Exercise: a potential contributing factor to the relationship between folate and dementia. J Am Geriatr Soc 2007;55(7):1095-8.
Full Text: Exclude - observational N<300

Mielke MM, Zandi PP, Sjogren M, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology 2005;64(10):1689-95.
Full Text: Exclude - <60% of dementia is AD

Milders M, Ietswaart M, Crawford JR, et al. Impairments in theory of mind shortly after traumatic brain injury and at 1-year follow-up. Neuropsychology 2006;20(4):400-8.
Full Text: Exclude - <80% >= 50 yo

Millar K, Nicoll JA, Thornhill S, et al. Long term neuropsychological outcome after head injury: relation to APOE genotype. J Neurol Neurosurg Psychiatry 2003;74(8):1047-52.
Full Text: Exclude - -<80% >= 50 yo

Min SK, Moon IW, Ko RW, et al. Effects of transdermal nicotine on attention and memory in healthy elderly non-smokers. Psychopharmacology (Berl) 2001;159(1):83-8.
Full Text: Exclude - AD/CD f/u < 1 yr

Mitchell JL, Cruickshanks KJ, Klein BE, et al. Postmenopausal hormone therapy and its association with cognitive impairment. Arch Intern Med 2003;163(20):2485-90.
Full Text: Exclude - outcomes unacceptably assessed

Mix JA, Crews WD, Jr. A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGb 761 in a sample of cognitively intact older adults: neuropsychological findings. Hum Psychopharmacol 2002;17(6):267-77.
Full Text: Exclude - AD/CD f/u < 1 yr

Miyasaka Y, Barnes ME, Petersen RC, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a community-based cohort. Eur Heart J 2007;28(16):1962-7.
Full Text: Exclude - risk factor out of scope

Mocchegiani E, Giacconi R, Costarelli L, et al. Zinc deficiency and IL-6 -174G/C polymorphism in old people from different European countries: effect of zinc supplementation. ZINCAGE study. Exp Gerontol 2008;43(5):433-44.
Full Text: Exclude - AD/CD f/u < 1 yr

Moceri VM, Kukull WA, Emanuel I, et al. Early-life risk factors and the development of Alzheimer's disease. Neurology 2000;54(2):415-20.
Full Text: Exclude - dementia @ baseline

Moffat SD, Zonderman AB, Harman SM, et al. The relationship between longitudinal declines in dehydroepiandrosterone sulfate concentrations and cognitive performance in older men. Arch Intern Med 2000;160(14):2193-8.
Full Text: Exclude - <80% are >= 50 yo

Moffat SD, Zonderman AB, Metter EJ, et al. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab 2002;87(11):5001-7.
Full Text: Exclude - observational N<300

Mooijaart SP, Gussekloo J, Frolich M, et al. Homocysteine, vitamin B-12, and folic acid and the risk of cognitive decline in old age: the Leiden 85-Plus study. Am J Clin Nutr 2005;82(4):866-71.
Full Text: Exclude - dementia @ baseline

Mori K, Inatomi S, Ouchi K, et al. Improving effects of the mushroom Yamabushitake (Hericium erinaceus) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. Phytother Res 2009;23(3):367-72.
Full Text: Exclude - AD/CD f/u < 1 yr

Morris MS, Jacques PF, Rosenberg IH, et al. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr 2007;85(1):193-200.
Full Text: Exclude - not longitudinal

Morrison MF, Redei E, TenHave T, et al. Dehydroepiandrosterone sulfate and psychiatric measures in a frail, elderly residential care population. Biol Psychiatry 2000;47(2):144-50.
Full Text: Exclude - selected population

Mortel KF, Meyer JS, Herod B, et al. Education and occupation as risk factors for dementias of the Alzheimer and ischemic vascular types. Dementia 1995;6(1):55-62.
Full Text: Exclude - dementia @ baseline

Mortimer JA, Snowdon DA, Markesbery WR. Small head circumference is associated with less education in persons at risk for Alzheimer disease in later life. Alzheimer Dis Assoc Disord 2008;22(3):249-54.
Full Text: Exclude - risk factor out of scope

Muldoon MF, Barger SD, Ryan C, et al. Effects of lovastatin on cognitive function and psychological well-being. Am J Med 2000;108(7):538-46.
Full Text: Exclude - <80% >= 50 yo

Muldoon MF, Ryan CM, Sereika SM, et al. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults.[see comment]. Am J Med 2004;117(11):823-9.
Full Text: Exclude - AD/CD f/u < 1 yr

Muldoon MF, Waldstein SR, Ryan CM, et al. Effects of six anti-hypertensive medications on cognitive performance. J Hypertens 2002;20(8):1643-52.
Full Text: Exclude - <80% >= 50 yo

Murray MD, Lane KA, Gao S, et al. Preservation of cognitive function with antihypertensive medications: a longitudinal analysis of a community-based sample of African Americans. Arch Intern Med 2002;162(18):2090-6.
Full Text: Exclude - <60 of dementia is AD

Natale V, Albertazzi P, Zini M, et al. Exploration of cyclical changes in memory and mood in postmenopausal women taking sequential combined oestrogen and progestogen preparations. BJOG 2001;108(3):286-90.
Full Text: Exclude - sample not randomly assigned

National Institute of Mental Health; University of Iowa. Cognitive Enhancers Explored with PET Imaging. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2009 Jul 09]. Available from: http://clinicaltrials.gov/ct/show/nct00042172. 2002.
Full Text: Exclude - no primary data

Nemetz PN, Leibson C, Naessens JM, et al. Traumatic brain injury and time to onset of Alzheimer's disease: a population-based study. Am J Epidemiol 1999;149(1):32-40.
Full Text: Exclude - outcomes unacceptably assessed

Newman GC, Bang H, Hussain SI, et al. Association of diabetes, homocysteine, and HDL with cognition and disability after stroke. Neurology 2007;69(22):2054-62.
Full Text: Exclude - outcomes unacceptably assessed

Newman MF, Grocott HP, Mathew JP, et al. Report of the substudy assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. Stroke 2001;32(12):2874-81.
Full Text: Exclude - risk factor out of scope

Nguyen HT, Black SA, Ray LA, et al. Predictors of decline in MMSE scores among older Mexican Americans. J Gerontol A Biol Sci Med Sci 2002;57(3):M181-5.
Full Text: Exclude - dementia @ baseline

Nilson LN, Backman L, Sallsten G, et al. Dose-related cognitive deficits among floor layers with previous heavy exposure to solvents. Arch Environ Health 2003;58(4):208-17.
Full Text: Exclude - observational N<300

Nilsson K, Gustafson L, Hultberg B. Relation between plasma homocysteine and Alzheimer's disease. Dement Geriatr Cogn Disord 2002;14(1):7-12.
Full Text: Exclude - dementia @ baseline

Nilsson K, Gustafson L, Hultberg B. Plasma homocysteine, cobalamin/folate status, and vascular disease in a large population of psychogeriatric patients. Dement Geriatr Cogn Disord 2006;22(4):358-66.
Full Text: Exclude - selected population

Nilsson P, Gullberg G, Ekesbo R, et al. No impaired cognitive function in treated patients with mild-moderate hypertension compared to normotensive controls. Blood Press 1998;7(4):209-13.
Full Text: Exclude - observational N<300

Nilsson SE, Johansson B, Takkinen S, et al. Does aspirin protect against Alzheimer's dementia? A study in a Swedish population-based sample aged > or =80 years. Eur J Clin Pharmacol 2003;59(4):313-9.
Full Text: Exclude - outcomes unacceptably assessed

Nilsson SE, Read S, Berg S, et al. Low systolic blood pressure is associated with impaired cognitive function in the oldest old: longitudinal observations in a population-based sample 80 years and older. Aging Clin Exp Res 2007;19(1):41-7.
Full Text: Exclude - dementia @ baseline

Nilsson SE, Takkinen S, Tryding N, et al. Association of biochemical values with morbidity in the elderly: a population-based Swedish study of persons aged 82 or more years. Scand J Clin Lab Invest 2003;63(7-8):457-66.
Full Text: Exclude - dementia @ baseline

Nishinaga M, Takata J, Okumiya K, et al. High morning home blood pressure is associated with a loss of functional independence in the community-dwelling elderly aged 75 years or older. Hypertens Res 2005;28(8):657-63.
Full Text: Exclude - not longitudinal

Nolin P. Executive memory dysfunctions following mild traumatic brain injury. J Head Trauma Rehabil 2006;21(1):68-75.
Full Text: Exclude - <80% are >= 50 yo

Nooyens AC, van Gelder BM, Verschuren WM. Smoking and cognitive decline among middle-aged men and women: the Doetinchem Cohort Study. Am J Public Health 2008;98(12):2244-50.
Full Text: Exclude - <80% >= 50 yo

Novartis. Efficacy and safety of Rivastigmine in patients

with mild cognitive impairment. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2009 Jul 09]. Available from: http://clinicaltrials.gov/ct/show/nct00134953. 2005.
Full Text: Exclude - no primary data

Nurk E, Refsum H, Tell GS, et al. Plasma total homocysteine and memory in the elderly: the Hordaland Homocysteine Study. Ann Neurol 2005;58(6):847-57.
Full Text: Exclude - not longitudinal

Nybo M, Andersen K, Sorensen GL, et al. Serum surfactant protein D is correlated to development of dementia and augmented mortality. Clin Immunol 2007;123(3):333-7.
Full Text: Exclude - risk factor out of scope

Nys GM, van Zandvoort MJ, de Kort PL, et al. The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. Neurology 2005;64(5):821-7.
Full Text: Exclude - AD/CD f/u < 1 yr

Obidi CS, Pugeda JP, Fan X, et al. Race moderates age-related cognitive decline in type 2 diabetes. Exp Aging Res 2008;34(2):114-25.
Full Text: Exclude - observational N<300

O'Brien JT, Lloyd A, McKeith I, et al. A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. Am J Psychiatry 2004;161(11):2081-90.
Full Text: Exclude - risk factor out of scope

O'Brien JT, Wiseman R, Burton EJ, et al. Cognitive associations of subcortical white matter lesions in older people. Ann N Y Acad Sci 2002;977:436-44.
Full Text: Exclude - risk factor out of scope

O'Dwyer ST, Burton NW, Pachana NA, et al. Protocol for Fit Bodies, Fine Minds: a randomized controlled trial on the affect of exercise and cognitive training on cognitive functioning in older adults. BMC Geriatr 2007;7:23.
Full Text: Exclude - AD/CD f/u < 1 yr

O'Hara R, Yesavage JA, Kraemer HC, et al. The APOE epsilon4 allele is associated with decline on delayed recall performance in community-dwelling older adults. J Am Geriatr Soc 1998;46(12):1493-8.
Full Text: Exclude - observational N<300

Okereke O, Hankinson SE, Hu FB, et al. Plasma C peptide level and cognitive function among older women without diabetes mellitus. Arch Intern Med 2005;165(14):1651-6.
Full Text: Exclude - risk factor out of scope

Okereke OI, Pollak MN, Hu FB, et al. Plasma C-peptide levels and rates of cognitive decline in older, community-dwelling women without diabetes. Psychoneuroendocrinology 2008;33(4):455-61.
Full Text: Exclude - risk factor out of scope

Ortega RM, Requejo AM, Andres P, et al. Dietary intake and cognitive function in a group of elderly people. Am J Clin Nutr 1997;66(4):803-9.
Full Text: Exclude - not longitudinal

Ostrosky-Solis F, Mendoza VU, Ardila A. Neuropsychological profile of patients with primary systemic hypertension. Int J Neurosci 2001;110(3-4):159-72.
Full Text: Exclude - observational N<300

Oswald WD, Rupprecht R, Gunzelmann T, et al. The SIMA-project: effects of 1 year cognitive and psychomotor training on cognitive abilities of the elderly. Behav Brain Res 1996;78(1):67-72.
Full Text: Exclude - sample not randomly assigned

Ott A, Breteler MM, de Bruyne MC, et al. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. Stroke 1997;28(2):316-21.
Full Text: Exclude - risk factor out of scope

Ott A, Stolk RP, Hofman A, et al. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia 1996;39(11):1392-7.
Full Text: Exclude - dementia @ baseline

Ousset PJ, Nourhashemi F, Reynish E, et al. Nutritional status is associated with disease progression in very mild Alzheimer disease. Alzheimer Dis Assoc Disord 2008;22(1):66-71.
Full Text: Exclude - dementia @ baseline

Ownby RL. Donepezil and vitamin E for mild cognitive impairment. Curr Psychiatry Rep 2006;8(1):9.
Full Text: Exclude - no primary data

Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. Arch Intern Med 1996;156(19):2213-7.
Full Text: Exclude - dementia @ baseline

Paile-Hyvarinen M, Raikkonen K, Kajantie E, et al. Impact of glucose metabolism and birth size on cognitive performance in elderly subjects. Diabetes Res Clin Pract 2009;83(3):379-86.
Full Text: Exclude - not longitudinal

Paillard-Borg S, Fratiglioni L, Winblad B, et al. Leisure activities in late life in relation to dementia risk: principal component analysis. Dement Geriatr Cogn Disord 2009;28(2):136-44.
Full Text: Exclude - <60% of dementia is AD

Paleologos M, Cumming RG, Lazarus R. Cohort study of vitamin C intake and cognitive impairment. Am J Epidemiol 1998;148(1):45-50.
Full Text: Exclude - observational N<300

Palmer K, Berger AK, Monastero R, et al. Predictors of progression from mild cognitive impairment to Alzheimer disease. Neurology 2007;68(19):1596-602.
Full Text: Exclude - observational N<300

Palsson S, Aevarsson O, Skoog I. Depression, cerebral atrophy, cognitive performance and incidence of dementia. Population study of 85-year-olds. Br J Psychiatry 1999;174:249-53.
Full Text: Exclude - observational N<300

Pan HA, Wang ST, Pai MC, et al. Cognitive function variations in postmenopausal women treated with continuous, combined HRT or tibolone. A comparison. J Reprod Med 2003;48(5):375-80.
Full Text: Exclude - AD/CD f/u < 1 yr

Pandav R, Dodge HH, DeKosky ST, et al. Blood pressure and cognitive impairment in India and the United States: a cross-national epidemiological study. Arch Neurol 2003;60(8):1123-8.
Full Text: Exclude - not longitudinal

Panegyres PK, Frencham K. Course and causes of suspected dementia in young adults: a longitudinal study. Am J Alzheimers Dis Other Demen 2007;22(1):48-56.
Full Text: Exclude - dementia @ baseline

Panza F, Capurso C, D'Introno A, et al. Impact of depressive symptoms on the rate of progression to dementia in patients affected by mild cognitive impairment. The Italian Longitudinal Study on Aging. Int J Geriatr Psychiatry 2008;23(7):726-34.
Full Text: Exclude - <60% of dementia is AD

Parale GP, Baheti NN, Kulkarni P, et al. Effects of atorvastatin on higher functions. Eur J Clin Pharmacol 2006;62(4):259-65.
Full Text: Exclude - non-Western country

Park H, Hildreth A, Thomson R, et al. Non-valvular atrial fibrillation and cognitive decline: a longitudinal cohort study. Age Ageing 2007;36(2):157-63.
Full Text: Exclude - risk factor out of scope

Parkkinen L, Kauppinen T, Pirttila T, et al. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. Ann Neurol 2005;57(1):82-91.
Full Text: Exclude - risk factor out of scope

Parnetti L, Ciuffetti G, Mercuri M, et al. Haemorheological pattern in initial mental deterioration: results of a long-term study using piracetam and pentoxifylline. Arch Gerontol Geriatr 1985;4(2):141-55.
Full Text: Exclude - dementia @ baseline

Parnetti L, Senin U, Carosi M, et al. Mental deterioration in old age: results of two multicenter, clinical trials with nimodipine. The Nimodipine Study Group. Clin Ther 1993;15(2):394-406.
Full Text: Exclude - dementia @ baseline

Parsons TD, Kratz KM, Thompson E, et al. Dhea supplementation and cognition in postmenopausal women. Int J Neurosci 2006;116(2):141-55.
Full Text: Exclude - AD/CD f/u < 1 yr

Patel M, Coshall C, Rudd AG, et al. Natural history of cognitive impairment after stroke and factors associated with its recovery. Clin Rehabil 2003;17(2):158-66.
Full Text: Exclude - observational N<300

Peacock JM, Folsom AR, Knopman DS, et al. Dietary antioxidant intake and cognitive performance in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) Study investigators. Public Health Nutr 2000;3(3):337-43.
Full Text: Exclude - not longitudinal

Pefanco MA, Kenny AM, Kaplan RF, et al. The effect of 3-year treatment with 0.25 mg/day of micronized 17beta-estradiol on cognitive function in older postmenopausal women. J Am Geriatr Soc 2007;55(3):426-31.
Full Text: Exclude - does not measure cognitive decline

Peila R, White LR, Petrovich H, et al. Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment: the Honolulu-Asia aging study. Stroke 2001;32(12):2882-9.
Full Text: Exclude - not longitudinal

Peretti CS, Gierski F, Harrois S. Cognitive skill learning in healthy older adults after 2 months of double-blind treatment with piribedil. Psychopharmacology (Berl) 2004;176(2):175-81.
Full Text: Exclude - AD/CD f/u < 1 yr

Perez-Stable EJ, Halliday R, Gardiner PS, et al. The effects of propranolol on cognitive function and quality of life: a randomized trial among patients with diastolic hypertension. Am J Med 2000;108(5):359-65.
Full Text: Exclude - < 80% >= 50 yo

Perrig WJ, Perrig P, Stahelin HB. The relation between antioxidants and memory performance in the old and very old. J Am Geriatr Soc 1997;45(6):718-24.
Full Text: Exclude - not longitudinal

Perrig-Chiello P, Perrig WJ, Ehrsam R, et al. The effects of resistance training on well-being and memory in elderly volunteers. Age Ageing 1998;27(4):469-75.
Full Text: Exclude - AD/CD f/u < 1 yr

Peters R, Beckett N, Geneva M, et al. Sociodemographic and lifestyle risk factors for incident dementia and cognitive decline in the HYVET. Age Ageing 2009;38(5):521-7.
Full Text: Exclude - non-Western country

Peters R, Beckett N, Nunes M, et al. A substudy protocol of the hypertension in the Very Elderly Trial assessing cognitive decline and dementia incidence (HYVET-COG) : An ongoing randomised, double-blind, placebo-controlled trial. Drugs Aging 2006;23(1):83-92.
Full Text: Exclude - methods paper

Petersen RC, Smith GE, Ivnik RJ, et al. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals.[erratum appears

in JAMA 1995 Aug 16;274(7):538]. JAMA 1995;273(16):1274-8.
Full Text: Exclude - observational N<300

Peterson SE, Stull MJ, Collins MW, et al. Neurocognitive function of emergency department patients with mild traumatic brain injury. Ann Emerg Med 2009;53(6):796-803 e1.
Full Text: Exclude - <80% >= 50 yo

Pettersen R, Saxby BK, Wyller TB. Poststroke urinary incontinence: one-year outcome and relationships with measures of attentiveness. J Am Geriatr Soc 2007;55(10):1571-7.
Full Text: Exclude - risk factor out of scope

Pignatti F, Rozzini R, Trabucchi M, et al. Physical activity and cognitive decline in elderly persons.[comment]. Arch Intern Med 2002;162(3):361-2.
Full Text: Exclude - Correspondence, inadequate outcomes

Piguet O, Cramsie J, Bennett HP, et al. Contributions of age and alcohol consumption to cerebellar integrity, gait and cognition in non-demented very old individuals. Eur Arch Psychiatry Clin Neurosci 2006;256(8):504-11.
Full Text: Exclude - observational N<300

Piguet O, Grayson DA, Creasey H, et al. Vascular risk factors, cognition and dementia incidence over 6 years in the Sydney Older Persons Study. Neuroepidemiology 2003;22(3):165-71.
Full Text: Exclude - observational N<300

Pipingas A, Silberstein RB, Vitetta L, et al. Improved cognitive performance after dietary supplementation with a Pinus radiata bark extract formulation. Phytother Res 2008;22(9):1168-74.
Full Text: Exclude - AD/CD f/u < 1 yr

Poirier J, Delisle MC, Quirion R, et al. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. Proc Natl Acad Sci U S A 1995;92(26):12260-4.
Full Text: Exclude - observational N<300

Ponholzer A, Madersbacher S, Rauchenwald M, et al. Serum androgen levels and their association to depression and Alzheimer dementia in a cohort of 75-year-old men over 5 years: results of the VITA study. Int J Impot Res 2009;21(3):187-91.
Full Text: Exclude - observational N<300

Potter GG, Helms MJ, Burke JR, et al. Job demands and dementia risk among male twin pairs. Alzheimer's & Dementia 2007;3:192-199.
Full Text: Exclude - data collected by proxy

Potter GG, Helms MJ, Plassman BL. Associations of job demands and intelligence with cognitive performance among men in late life. Neurology 2008;70(19 Pt 2):1803-8.
Full Text: Exclude - not longitudinal

Pradignac A, Schlienger JL, Velten M, et al. Relationships between macronutrient intake, handicaps, and cognitive impairments in free living elderly people. Aging (Milano) 1995;7(1):67-74.
Full Text: Exclude - not longitudinal

Presse N, Shatenstein B, Kergoat MJ, et al. Low vitamin K intakes in community-dwelling elders at an early stage of Alzheimer's disease. J Am Diet Assoc 2008;108(12):2095-9.
Full Text: Exclude - observational N<300

Prohaska TR, Eisenstein AR, Satariano WA, et al. Walking and the preservation of cognitive function in older populations. Gerontologist 2009;49 Suppl 1:S86-93.
Full Text: Exclude - not longitudinal

Psaltopoulou T, Kyrozis A, Stathopoulos P, et al. Diet, physical activity and cognitive impairment among elders: the EPIC-Greece cohort (European Prospective Investigation into Cancer and Nutrition). Public Health Nutr 2008;11(10):1054-62.
Full Text: Exclude - not longitudinal

Qiu C, Winblad B, Marengoni A, et al. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. Arch Intern Med 2006;166(9):1003-8.
Full Text: Exclude - risk factor out of scope

Rabbitt P, Lunn M, Ibrahim S, et al. Unhappiness, health and cognitive ability in old age. Psychol Med 2008;38(2):229-36.
Full Text: Exclude - Q2 continuous data only

Rammsayer TH. Effects of pharmacologically induced changes in NMDA receptor activity on human timing and sensorimotor performance. Brain Res 2006;1073-1074:407-16.
Full Text: Exclude - <60% of dementia is AD

Ramos MI, Allen LH, Mungas DM, et al. Low folate status is associated with impaired cognitive function and dementia in the Sacramento Area Latino Study on Aging. Am J Clin Nutr 2005;82(6):1346-52.
Full Text: Exclude - not longitudinal

Rapoport M, Wolf U, Herrmann N, et al. Traumatic brain injury, Apolipoprotein E-epsilon4, and cognition in older adults: a two-year longitudinal study. J Neuropsychiatry Clin Neurosci 2008;20(1):68-73.
Full Text: Exclude - observational N<300

Rapoport MJ, Herrmann N, Shammi P, et al. Outcome after traumatic brain injury sustained in older adulthood: a one-year longitudinal study. Am J Geriatr Psychiatry 2006;14(5):456-65.
Full Text: Exclude - observational N<300

Rapp S, Brenes G, Marsh AP. Memory enhancement training for older adults with mild cognitive impairment: a preliminary study. Aging Ment Health 2002;6(1):5-11.

Full Text: Exclude - AD/CD f/u < 1 yr

Rasmussen LS, O'Brien JT, Silverstein JH, et al. Is peri-operative cortisol secretion related to post-operative cognitive dysfunction? Acta Anaesthesiol Scand 2005;49(9):1225-31.
Full Text: Exclude - risk factor out of scope

Rastas S, Verkkoniemi A, Polvikoski T, et al. Atrial fibrillation, stroke, and cognition: a longitudinal population-based study of people aged 85 and older. Stroke 2007;38(5):1454-60.
Full Text: Exclude - <60% of dementia is AD

Ravaglia G, Forti P, Lucicesare A, et al. Plasma tocopherols and risk of cognitive impairment in an elderly Italian cohort. Am J Clin Nutr 2008;87(5):1306-13.
Full Text: Exclude - risk factor out of scope

Ravaglia G, Forti P, Maioli F, et al. Endogenous sex hormones as risk factors for dementia in elderly men and women. J Gerontol A Biol Sci Med Sci 2007;62(9):1035-41.
Full Text: Exclude - risk factor out of scope

Ravaglia G, Forti P, Maioli F, et al. Blood inflammatory markers and risk of dementia: The Conselice Study of Brain Aging. Neurobiol Aging 2007;28(12):1810-20.
Full Text: Exclude - risk factor out of scope

Ravaglia G, Forti P, Maioli F, et al. Incidence and etiology of dementia in a large elderly Italian population. Neurology 2005;64(9):1525-30.
Full Text: Exclude - risk factor out of scope

Ravaglia G, Forti P, Maioli F, et al. Conversion of mild cognitive impairment to dementia: predictive role of mild cognitive impairment subtypes and vascular risk factors. Dement Geriatr Cogn Disord 2006;21(1):51-8.
Full Text: Exclude - observational N<300

Ravaglia G, Forti P, Maioli F, et al. Education, occupation, and prevalence of dementia: findings from the Conselice study. Dement Geriatr Cogn Disord 2002;14(2):90-100.
Full Text: Exclude - not longitudinal

Ravaglia G, Forti P, Maioli F, et al. Homocysteine and cognitive performance in healthy elderly subjects. Arch Gerontol Geriatr Suppl 2004(9):349-57.
Full Text: Exclude - observational N<300

Raymont V, Greathouse A, Reding K, et al. Demographic, structural and genetic predictors of late cognitive decline after penetrating head injury. Brain 2008;131(Pt 2):543-58.
Full Text: Exclude - risk factor out of scope

Raynaud-Simon A, Lafont S, Berr C, et al. Plasma insulin-like growth factor I levels in the elderly: relation to plasma dehydroepiandrosterone sulfate levels, nutritional status, health and mortality. Gerontology 2001;47(4):198-206.
Full Text: Exclude - risk factor out of scope

Raz N, Rodrigue KM, Kennedy KM, et al. Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. Neuropsychology 2007;21(2):149-57.
Full Text: Exclude - observational N<300

Reinprecht F, Elmstahl S, Janzon L, et al. Hypertension and changes of cognitive function in 81-year-old men: a 13-year follow-up of the population study "Men born in 1914", Sweden. J Hypertens 2003;21(1):57-66.
Full Text: Exclude - observational N<300

Reischies FM, Neu P. Comorbidity of mild cognitive disorder and depression--a neuropsychological analysis. Eur Arch Psychiatry Clin Neurosci 2000;250(4):186-93.
Full Text: Exclude - observational N<300

Renvall MJ, Spindler AA, Ramsdell JW, et al. Nutritional status of free-living Alzheimer's patients. Am J Med Sci 1989;298(1):20-7.
Full Text: Exclude - dementia @ baseline

Resnick SM, Coker LH, Maki PM, et al. The Women's Health Initiative Study of Cognitive Aging (WHISCA): a randomized clinical trial of the effects of hormone therapy on age-associated cognitive decline. Clin Trials 2004;1(5):440-50.
Full Text: Exclude - methods paper

Reynolds CA, Gatz M, Berg S, et al. Genotype-environment interactions: cognitive aging and social factors. Twin Res Hum Genet 2007;10(2):241-54.
Full Text: Exclude - observational N<300

Richard F, Berr C, Amant C, et al. Effect of the angiotensin I-converting enzyme I/D polymorphism on cognitive decline. The EVA Study Group. Neurobiol Aging 2000;21(1):75-80.
Full Text: Exclude - risk factor out of scope

Richards M, Jarvis MJ, Thompson N, et al. Cigarette smoking and cognitive decline in midlife: evidence from a prospective birth cohort study. Am J Public Health 2003;93(6):994-8.
Full Text: Exclude - <80% >= 50 yo

Richards M, Meade TW, Peart S, et al. Is there any evidence for a protective effect of antithrombotic medication on cognitive function in men at risk of cardiovascular disease? Some preliminary findings. J Neurol Neurosurg Psychiatry 1997;62(3):269-72.
Full Text: Exclude - risk factor out of scope

Richards M, Shipley B, Fuhrer R, et al. Cognitive ability in childhood and cognitive decline in mid-life: longitudinal birth cohort study. BMJ 2004;328(7439):552.
Full Text: Exclude - <80% >= 50 yo

Richards M, Wadsworth ME. Long term effects of early adversity on cognitive function. Arch Dis Child 2004;89(10):922-7.
Full Text: Exclude - not longitudinal

Richards SS, Emsley CL, Roberts J, et al. The association between vascular risk factor-mediating medications and cognition and dementia diagnosis in a community-based sample of African-Americans. J Am Geriatr Soc 2000;48(9):1035-41.
Full Text: Exclude - not longitudinal

Riemersma-van der Lek RF, Swaab DF, Twisk J, et al. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. JAMA 2008;299(22):2642-55.
Full Text: Exclude - dementia @ baseline

Robbins MA, Elias MF, Budge MM, et al. Homocysteine, type 2 diabetes mellitus, and cognitive performance: The Maine-Syracuse Study. Clin Chem Lab Med 2005;43(10):1101-6.
Full Text: Exclude - not longitudinal

Robbins MA, Elias MF, Elias PK, et al. Blood pressure and cognitive function in an African-American and a Caucasian-American sample: the Maine-Syracuse Study. Psychosom Med 2005;67(5):707-14.
Full Text: Exclude - not longitudinal

Roberts RO, Geda YE, Knopman DS, et al. Association of duration and severity of diabetes mellitus with mild cognitive impairment. Arch Neurol 2008;65(8):1066-73.
Full Text: Exclude - not longitudinal

Robertson-Tchabo EA, Arenberg D, Tobin JD, et al. A longitudinal study of cognitive performance in noninsulin dependent (type II) diabetic men. Exp Gerontol 1986;21(4-5):459-67.
Full Text: Exclude - observational N<300

Rockwood K, Ebly E, Hachinski V, et al. Presence and treatment of vascular risk factors in patients with vascular cognitive impairment. Arch Neurol 1997;54(1):33-9.
Full Text: Exclude - dementia @ baseline

Rockwood K, Howlett S, Fisk J, et al. Lipid-lowering agents and the risk of cognitive impairment that does not meet criteria for dementia, in relation to apolipoprotein E status. Neuroepidemiology 2007;29(3-4):201-7.
Full Text: Exclude - not longitudinal

Rockwood K, Kirkland S, Hogan D, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurol 2002;59(2):223-7.
Full Text: Exclude - not longitudinal

Rondanelli M, Trotti R, Opizzi A, et al. Relationship among nutritional status, pro/antioxidant balance and cognitive performance in a group of free-living healthy elderly. Minerva Med 2007;98(6):639-45.
Full Text: Exclude - observational N<300

Ronnemaa E, Zethelius B, Sundelof J, et al. Impaired insulin secretion increases the risk of Alzheimer disease. Neurology 2008;71(14):1065-71.
Full Text: Exclude - risk factor out of scope

Ronnlund M, Nyberg L, Backman L, et al. Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. Psychol Aging 2005;20(1):3-18.
Full Text: Exclude - risk factor out of scope

Roriz-Cruz M, Rosset I, Wada T, et al. Cognitive impairment and frontal-subcortical geriatric syndrome are associated with metabolic syndrome in a stroke-free population. Neurobiol Aging 2007;28(11):1723-36.
Full Text: Exclude - non-Western country

Rosenblatt A, Mehta KM, Romanoski A, et al. Major depression and cognitive decline after 11.5 years: findings from the ECA study. J Nerv Ment Dis 2003;191(12):827-30.
Full Text: Exclude - <80% >= 50 yo

Rotkiewicz-Piorun AM, Al Snih S, Raji MA, et al. Cognitive decline in older Mexican Americans with diabetes. J Natl Med Assoc 2006;98(11):1840-7.
Full Text: Exclude - non-Western country

Rowan E, Morris CM, Stephens S, et al. Impact of hypertension and apolipoprotein E4 on poststroke cognition in subjects >75 years of age. Stroke 2005;36(9):1864-8.
Full Text: Exclude - not applicable population

Rowan EN, Dickinson HO, Stephens S, et al. Homocysteine and post-stroke cognitive decline. Age Ageing 2007;36(3):339-43.
Full Text: Exclude - observational N<300

Rozzini L, Chilovi BV, Bertoletti E, et al. Angiotensin converting enzyme (ACE) inhibitors modulate the rate of progression of amnestic mild cognitive impairment. Int J Geriatr Psychiatry 2006;21(6):550-5.
Full Text: Exclude - observational N<300

Rozzini L, Costardi D, Chilovi BV, et al. Efficacy of cognitive rehabilitation in patients with mild cognitive impairment treated with cholinesterase inhibitors. Int J Geriatr Psychiatry 2007;22(4):356-60.
Full Text: Exclude - sample not randomly assigned

Rozzini R, Ferrucci L, Losonczy K, et al. Protective effect of chronic NSAID use on cognitive decline in older persons. J Am Geriatr Soc 1996;44(9):1025-9.
Full Text: Exclude - SPMSQ single test

Ryglewicz D, Rodo M, Kunicki PK, et al. Plasma antioxidant activity and vascular dementia. J Neurol Sci 2002;203-204:195-7.
Full Text: Exclude - dementia @ baseline

Saag KG, Rubenstein LM, Chrischilles EA, et al. Nonsteroidal antiinflammatory drugs and cognitive decline

in the elderly. J Rheumatol 1995;22(11):2142-7.
Full Text: Exclude - dementia @ baseline

Sabia S, Kivimaki M, Shipley MJ, et al. Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. Am J Clin Nutr 2009;89(2):601-7.
Full Text: Exclude - not longitudinal

Sabia S, Nabi H, Kivimaki M, et al. Health behaviors from early to late midlife as predictors of cognitive function: The Whitehall II study. Am J Epidemiol 2009;170(4):428-37.
Full Text: Exclude - not longitudinal

Sachdev PS, Brodaty H, Valenzuela MJ, et al. Clinical determinants of dementia and mild cognitive impairment following ischaemic stroke: the Sydney Stroke Study. Dement Geriatr Cogn Disord 2006;21(5-6):275-83.
Full Text: Exclude - <60% of dementia is AD

Sachs-Ericsson N, Blazer DG. Racial differences in cognitive decline in a sample of community-dwelling older adults: the mediating role of education and literacy. Am J Geriatr Psychiatry 2005;13(11):968-75.
Full Text: Exclude - SPMSQ single test

Sachs-Ericsson N, Joiner T, Plant EA, et al. The influence of depression on cognitive decline in community-dwelling elderly persons. Am J Geriatr Psychiatry 2005;13(5):402-8.
Full Text: Exclude - SPMSQ single test

Sacktor N, Gray S, Kawas C, et al. Systolic blood pressure within an intermediate range may reduce memory loss in an elderly hypertensive cohort. J Geriatr Psychiatry Neurol 1999;12(1):1-6.
Full Text: Exclude - observational N<300

Saczynski JS, Jonsdottir MK, Garcia ME, et al. Cognitive impairment: an increasingly important complication of type 2 diabetes: the age, gene/environment susceptibility--Reykjavik study. Am J Epidemiol 2008;168(10):1132-9.
Full Text: Exclude - not longitudinal

Salloway S, Correia S, Richardson S. Key lessons learned from short-term treatment trials of cholinesterase inhibitors for amnestic MCI. Int Psychogeriatr 2008;20(1):40-6.
Full Text: Exclude - no primary data

Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. Neurology 2004;63(4):651-7.
Full Text: Exclude - not longitufinal SB-AD/CD f/u < 1 yr

Salminen EK, Portin RI, Koskinen AI, et al. Estradiol and cognition during androgen deprivation in men with prostate carcinoma. Cancer 2005;103(7):1381-7.
Full Text: Exclude - not applicable population

Samieri C, Feart C, Letenneur L, et al. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk. Am J Clin Nutr 2008;88(3):714-21.
Full Text: Exclude - <60% of dementia is AD

Santanello NC, Barber B, Applegate W, et al. Effect of pharmacologic lipid lowering on health-related quality of life in older persons: results from the Cholesterol Reduction in Seniors Program (CRISP) Pilot Study. J Am Geriatr Soc 1997;45(1):8-14.
Full Text: Exclude - AD/VD f/u < 1 year

Saxby BK, Harrington F, McKeith IG, et al. Effects of hypertension on attention, memory, and executive function in older adults. Health Psychol 2003;22(6):587-91.
Full Text: Exclude - not longitudinal

Scarmeas N, Albert SM, Manly JJ, et al. Education and rates of cognitive decline in incident Alzheimer's disease. J Neurol Neurosurg Psychiatry 2006;77(3):308-16.
Full Text: Exclude - dementia @ baseline

Scarmeas N, Stern Y, Mayeux R, et al. Mediterranean diet, Alzheimer disease, and vascular mediation. Arch Neurol 2006;63(12):1709-17.
Full Text: Exclude - not longitudinal

Schantz SL, Sweeney AM, Gardiner JC, et al. Neuropsychological assessment of an aging population of Great Lakes fisheaters. Toxicol Ind Health 1996;12(3-4):403-17.
Full Text: Exclude - not longitudinal

Schippling S, Kontush A, Arlt S, et al. Increased lipoprotein oxidation in Alzheimer's disease. Free Radic Biol Med 2000;28(3):351-60.
Full Text: Exclude - dementia @ baseline

Schmand B, Jonker C, Geerlings MI, et al. Subjective memory complaints in the elderly: depressive symptoms and future dementia. Br J Psychiatry 1997;171:373-6.
Full Text: Exclude - AD f/u < 2 yr

Schmand B, Smit J, Lindeboom J, et al. Low education is a genuine risk factor for accelerated memory decline and dementia. J Clin Epidemiol 1997;50(9):1025-33.
Full Text: Exclude - <60% of dementia is AD

Schmand B, Smit JH, Geerlings MI, et al. The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. Psychol Med 1997;27(6):1337-44.
Full Text: Exxclude - <60% of dementia is AD

Schmidt R, Fazekas F, Koch M, et al. Magnetic resonance imaging cerebral abnormalities and neuropsychologic test performance in elderly hypertensive subjects. A case-control study. Arch Neurol 1995;52(9):905-10.
Full Text: Exclude - observational N<300

Schmidt R, Hayn M, Reinhart B, et al. Plasma antioxidants and cognitive performance in middle-aged and older adults: results of the Austrian Stroke Prevention Study. J Am Geriatr Soc 1998;46(11):1407-10.
Full Text: Exclude - not longitudinal

Schoeman R, Carey P, Seedat S. Trauma and posttraumatic stress disorder in South African adolescents: a case-control study of cognitive deficits. J Nerv Ment Dis 2009;197(4):244-50.
Full Text: Exclude - risk factor out of scope

Scott RD, Kritz-Silverstein D, Barrett-Connor E, et al. The association of non-insulin-dependent diabetes mellitus and cognitive function in an older cohort. J Am Geriatr Soc 1998;46(10):1217-22.
Full Text: Exclude - not longitudinal

Scuteri A, Coluccia R, Castello L, et al. Left ventricular mass increase is associated with cognitive decline and dementia in the elderly independently of blood pressure. Eur Heart J 2009;30(12):1525-9.
Full Text: Exclude - not longitudinal

Scuteri A, Palmieri L, Lo Noce C, et al. Age-related changes in cognitive domains. A population-based study. Aging Clin Exp Res 2005;17(5):367-73.
Full Text: Exclude - not longitudinal

Scuteri A, Tesauro M, Appolloni S, et al. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. J Hypertens 2007;25(5):1035-40.
Full Text: Exclude - dementia @ baseline

Seeman TE, Huang MH, Bretsky P, et al. Education and APOE-e4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. J Gerontol B Psychol Sci Soc Sci 2005;60(2):P74-83.
Full Text: Exclude - SPMSQ single test

Seeman TE, McEwen BS, Singer BH, et al. Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. J Clin Endocrinol Metab 1997;82(8):2458-65.
Full Text: Exclude - risk factor out of scope

Seidler A, Bernhardt T, Nienhaus A, et al. Association between the psychosocial network and dementia--a case-control study. J Psychiatr Res 2003;37(2):89-98.
Full Text: Exclude - dementia @ baseline

Selhub J, Morris MS, Jacques PF, et al. Folate-vitamin B-12 interaction in relation to cognitive impairment, anemia, and biochemical indicators of vitamin B-12 deficiency. Am J Clin Nutr 2009;89(2):702S-6S.
Full Text: Exclude - not longitudinal

Senanarong V, Jamjumrus P, Harnphadungkit K, et al. Risk factors for dementia and impaired cognitive status in Thai elderly. J Med Assoc Thai 2001;84(4):468-74.
Full Text: Exclude - non-Western country

Sendelbach S, Lindquist R, Watanuki S, et al. Correlates of neurocognitive function of patients after off-pump coronary artery bypass surgery. Am J Crit Care 2006;15(3):290-8.
Full Text: Exclude - risk factor out of scope

Serra JA, Marschoff ER, Dominguez RO, et al. Oxidative stress in Alzheimer's and vascular dementias: masking of the antioxidant profiles by a concomitant Type II diabetes mellitus condition. J Neurol Sci 2004;218(1-2):17-24.
Full Text: Exclude - dementia @ baseline

Serrano S, Domingo J, Rodriguez-Garcia E, et al. Frequency of cognitive impairment without dementia in patients with stroke: a two-year follow-up study. Stroke 2007;38(1):105-10.
Full Text: Exclude - not longitudinal

Seshadri S, Wolf PA, Beiser A, et al. Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. Neurology 1997;49(6):1498-504.
Full Text: Exclude - risk factor out of scope

Shadlen MF, Siscovick D, Fitzpatrick AL, et al. Education, cognitive test scores, and black-white differences in dementia risk. J Am Geriatr Soc 2006;54(6):898-905.
Full Text: Exclude - <60% of dementia is AD

Shahinian VB, Kuo YF, Freeman JL, et al. Risk of the "androgen deprivation syndrome" in men receiving androgen deprivation for prostate cancer. Arch Intern Med 2006;166(4):465-71.
Full Text: Exclude - not applicable population

Shapiro AP, Nixon P, Miller RE, et al. Behavioural consequences of hypertension: effects of age and type of antihypertensive agent. J Hum Hypertens 1989;3(6):435-42.
Full Text: Exclude - observational N<300

Shatenstein B, Kergoat MJ, Reid I. Poor nutrient intakes during 1-year follow-up with community-dwelling older adults with early-stage Alzheimer dementia compared to cognitively intact matched controls. J Am Diet Assoc 2007;107(12):2091-9.
Full Text: Exclude - dementia @ baseline

Shepherd CE, Piguet O, Broe GA, et al. Histocompatibility antigens, aspirin use and cognitive performance in non-demented elderly subjects. J Neuroimmunol 2004;148(1-2):178-82.
Full Text: Exclude - observational N<300

Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. Control Clin Trials 1998;19(6):604-21.
Full Text: Exclude - methods paper

Simons LA, Simons J, McCallum J, et al. Lifestyle factors and risk of dementia: Dubbo Study of the elderly. Med J Aust 2006;184(2):68-70.
Full Text: Exclude - <60% of dementia is AD

Singh-Manoux A, Marmot M. High blood pressure was

associated with cognitive function in middle-age in the Whitehall II study. J Clin Epidemiol 2005;58(12):1308-15.
Full Text: Exclude - not longitudinal

Sink KM, Leng X, Williamson J, et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. Arch Intern Med 2009;169(13):1195-202.
Full Text: Exclude - outcomes inadequately assessed

Sinoff G, Werner P. Anxiety disorder and accompanying subjective memory loss in the elderly as a predictor of future cognitive decline. Int J Geriatr Psychiatry 2003;18(10):951-9.
Full Text: Exclude - observational N<300

Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. Lancet 1996;347(9009):1141-5.
Full Text: Exclude - <60% of dementia is AD

Slooter AJ, Cruts M, Ott A, et al. The effect of APOE on dementia is not through atherosclerosis: the Rotterdam Study.[see comment]. Neurology 1999;53(7):1593-5.
Full Text: Exclude - <60% of dementia is AD

Small GW, La Rue A, Komo S, et al. Mnemonics usage and cognitive decline in age-associated memory impairment. Int Psychogeriatr 1997;9(1):47-56.
Full Text: Exclude - observational N<300

Small GW, Siddarth P, Silverman DH, et al. Cognitive and cerebral metabolic effects of celecoxib versus placebo in people with age-related memory loss: randomized controlled study. Am J Geriatr Psychiatry 2008;16(12):999-1009.
Full Text: Exclude - RCT N < 50

Smith CD, Walton A, Loveland AD, et al. Memories that last in old age: motor skill learning and memory preservation. Neurobiol Aging 2005;26(6):883-90.
Full Text: Exclude - observational N<300

Smith EE, Egorova S, Blacker D, et al. Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. Arch Neurol 2008;65(1):94-100.
Full Text: Exclude - observational N<300

Smith GE, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. J Am Geriatr Soc 2009;57(4):594-603.
Full Text: Exclude - AD/CD f/u < 1 yr

Smyth KA, Fritsch T, Cook TB, et al. Worker functions and traits associated with occupations and the development of AD. Neurology 2004;63(3):498-503.
Full Text: Exclude - not longitudinal

Snowdon DA, Kemper SJ, Mortimer JA, et al. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study.[see comment]. JAMA 1996;275(7):528-32.
Full Text: Exclude - observational N<300

Sobel E, Davanipour Z, Sulkava R, et al. Occupations with exposure to electromagnetic fields: a possible risk factor for Alzheimer's disease. Am J Epidemiol 1995;142(5):515-24.
Full Text: Exclude - dementia @ baseline

Sole-Padulles C, Bartres-Faz D, Junque C, et al. Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2009;30(7):1114-24.
Full Text: Exclude - risk factor out of scope

Solfrizzi V, Colacicco AM, D'Introno A, et al. Dietary fatty acids intakes and rate of mild cognitive impairment. The Italian Longitudinal Study on Aging. Exp Gerontol 2006;41(6):619-27.
Full Text: Exclude - observational N<300

Solfrizzi V, Colacicco AM, D'Introno A, et al. Dietary intake of unsaturated fatty acids and age-related cognitive decline: a 8.5-year follow-up of the Italian Longitudinal Study on Aging. Neurobiol Aging 2006;27(11):1694-704.
Full Text: Exclude - observational N<300

Solfrizzi V, Panza F, Torres F, et al. High monounsaturated fatty acids intake protects against age-related cognitive decline. Neurology 1999;52(8):1563-9.
Full Text: Exclude - observational N<300

Solomon PR, Adams F, Silver A, et al. Ginkgo for memory enhancement: a randomized controlled trial. JAMA 2002;288(7):835-40.
Full Text: Exclude - AD/CD f/u < 1 yr

Solomon S, Hotchkiss E, Saravay SM, et al. Impairment of memory function by antihypertensive medication. Arch Gen Psychiatry 1983;40(10):1109-12.
Full Text: Exclude - observational N<300

Sonnen JA, Larson EB, Brickell K, et al. Different patterns of cerebral injury in dementia with or without diabetes. Arch Neurol 2009;66(3):315-22.
Full Text: Exclude - observational N<300

Sparks D, Kryscio R, Sabbagh M, et al. Reduced risk of incident AD with elective statin use in a clinical trial cohort. Curr Alzheimer Res 2008;5(4):416-21.
Full Text: Exclude - dementia @ baseline

Sparks D, Petanceska S, Sabbagh M, et al. Cholesterol, copper and Abeta in controls, MCI, AD and the AD cholesterol-lowering treatment trial (ADCLT). Curr Alzheimer Res 2005;2(5):527-39.
Full Text: Exclude - not longitudinal

Spindler AA, Renvall MA. Nutritional status and psychometric test scores in cognitively impaired elders. Ann N Y Acad Sci 1989;561:167-77.

Full Text: Exclude - dementia @ baseline

Spinks H, Dalgleish T. Attentional processing and levels of symptomatology in Seasonal Affective Disorder (SAD): a preliminary longitudinal study. J Affect Disord 2001;62(3):229-32.
Full Text: Exclude - observational N<300

Stanley TO, Mackensen GB, Grocott HP, et al. The impact of postoperative atrial fibrillation on neurocognitive outcome after coronary artery bypass graft surgery. Anesth Analg 2002;94(2):290-5, table of contents.
Full Text: Exclude - risk factor out of scope

Starr J, McGurn B, Whiteman M, et al. Life long changes in cognitive ability are associated with prescribed medications in old age. Int J Geriatr Psychiatry 2004;19(4):327-32.
Full Text: Exclude - not longitudinal

Starr JM, Deary IJ, Fox H, et al. Blood pressure and cognition in the Aberdeen 1936 birth cohort. Gerontology 2007;53(6):432-7.
Full Text: Exclude - not longitudinal

Starr JM, Deary IJ, Fox HC, et al. Smoking and cognitive change from age 11 to 66 years: a confirmatory investigation. Addict Behav 2007;32(1):63-8.
Full Text: Exclude - observational N<300

Starr JM, Deary IJ, Inch S, et al. Age-associated cognitive decline in healthy old people. Age Ageing 1997;26(4):295-300.
Full Text: Exclude - not longitudinal

Starr JM, Deary IJ, Inch S, et al. Blood pressure and cognitive decline in healthy old people. J Hum Hypertens 1997;11(12):777-81.
Full Text: Exclude - not general population

Starr JM, McGurn B, Whiteman M, et al. Life long changes in cognitive ability are associated with prescribed medications in old age. Int J Geriatr Psychiatry 2004;19(4):327-32.
Full Text: Exclude - outcomes unacceptably assessed

Starr JM, Whalley LJ. Differential cognitive outcomes in the Hypertensive Old People in Edinburgh study. J Neurol Sci 2005;229-230:103-7.
Full Text: Exclude - AD/CD f/u < 1 yr

Starr JM, Whalley LJ, Deary IJ. The effects of antihypertensive treatment on cognitive function: results from the HOPE study. J Am Geriatr Soc 1996;44(4):411-5.
Full Text: Exclude - AD/CD f/u < 1 yr

Stefanick ML, Cochrane BB, Hsia J, et al. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. Ann Epidemiol 2003;13(9 Suppl):S78-86.
Full Text: Exclude - outcomes not AD/CD

Steffens DC, Welsh-Bohmer KA, Burke JR, et al. Methodology and preliminary results from the neurocognitive outcomes of depression in the elderly study. J Geriatr Psychiatry Neurol 2004;17(4):202-11.
Full Text: Exclude - not applicable population

Stepaniuk J, Ritchie LJ, Tuokko H. Neuropsychiatric impairments as predictors of mild cognitive impairment, dementia, and Alzheimer's disease. Am J Alzheimers Dis Other Demen 2008;23(4):326-33.
Full Text: Exclude - risk factor out of scope

Stephens R, Sreenivasan B. Neuropsychological effects of long-term low-level organophosphate exposure in orchard sprayers in England. Arch Environ Health 2004;59(11):566-74.
Full Text: Exclude - observational N<300

Stewart R, Hirani V. Dental health and cognitive impairment in an English national survey population. J Am Geriatr Soc 2007;55(9):1410-4.
Full Text: Exclude - risk factor out of scope

Stewart R, Masaki K, Xue QL, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol 2005;62(1):55-60.
Full Text: Exclude - risk factor out of scope

Stewart R, Prince M, Mann A. Age, vascular risk, and cognitive decline in an older, British, African-Caribbean population. J Am Geriatr Soc 2003;51(11):1547-53.
Full Text: Exclude - observational N<300

Sturmer T, Glynn RJ, Field TS, et al. Aspirin use and cognitive function in the elderly. Am J Epidemiol 1996;143(7):683-91.
Full Text: Exclude - SPMSQ single test

Suhr JA, Stewart JC, France CR. The relationship between blood pressure and cognitive performance in the Third National Health and Nutrition Examination Survey (NHANES III). Psychosom Med 2004;66(3):291-7.
Full Text: Exclude - <80% >= 50 yo

Sulbaran TA, Silva ER, Maestre G. Isolated systolic hypertension: a new challenge in medicine. J Hum Hypertens 2002;16 Suppl 1:S44-7.
Full Text: Exclude - non-Western country

Summers M, Oliver K, Coombes JS, et al. Effect of atorvastatin on cognitive function in patients from the Lipid Lowering and Onset of Renal Disease (LORD) trial. Pharmacotherapy 2007;27(2):183-90.
Full Text: Exclude - AD/CD f/u < 1 year

Sun Q, Townsend MK, Okereke OI, et al. Adiposity and weight change in mid-life in relation to healthy survival after age 70 in women: prospective cohort study. BMJ 2009;339:b3796.
Full Text: Exclude - AD/CD unacceptably assessed

Sundelof J, Arnlov J, Ingelsson E, et al. Serum cystatin C and the risk of Alzheimer disease in elderly men. Neurology 2008;71(14):1072-9.
Full Text: Exclude - risk factor out of scope

Swan GE, Carmelli D, Larue A. Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. Stroke 1998;29(11):2334-40.
Full Text: Exclude - not longitudinal

Sweetow RW, Sabes JH. The need for and development of an adaptive Listening and Communication Enhancement (LACE) Program. J Am Acad Audiol 2006;17(8):538-58.
Full Text: Exclude - risk factor out of scope

Sze KH, Sim TC, Wong E, et al. Effect of nimodipine on memory after cerebral infarction. Acta Neurol Scand 1998;97(6):386-92.
Full Text: Exclude - risk factor out of scope

Szekely CA, Green RC, Breitner JC, et al. No advantage of A beta 42-lowering NSAIDs for prevention of Alzheimer dementia in six pooled cohort studies. Neurology 2008;70(24):2291-8.
Full Text: Exclude - not longitudinal

Tabbarah M, Crimmins EM, Seeman TE. The relationship between cognitive and physical performance: MacArthur Studies of Successful Aging. J Gerontol A Biol Sci Med Sci 2002;57(4):M228-35.
Full Text: Exclude - outcomes unacceptably assessed

Tan ZS, Beiser A, Vasan RS, et al. Thyroid function and the risk of Alzheimer disease: the Framingham Study. Arch Intern Med 2008;168(14):1514-20.
Full Text: Exclude - risk factor out of scope

Tan ZS, Seshadri S, Beiser A, et al. Bone mineral density and the risk of Alzheimer disease. Arch Neurol 2005;62(1):107-11.
Full Text: Exclude - risk factor out of scope

Tang MX, Maestre G, Tsai WY, et al. Effect of age, ethnicity, and head injury on the association between APOE genotypes and Alzheimer's disease. Ann N Y Acad Sci 1996;802:6-15.
Full Text: Exclude - dementia @ baseline

Tang WK, Chan SS, Chiu HF, et al. Frequency and determinants of prestroke dementia in a Chinese cohort. J Neurol 2004;251(5):604-8.
Full Text: Exclude - <60% of dementia is AD

Tanne D, Freimark D, Poreh A, et al. Cognitive functions in severe congestive heart failure before and after an exercise training program. Int J Cardiol 2005;103(2):145-9.
Full Text: Exclude - risk factor out of scope

Tedesco MA, Ratti G, Mennella S, et al. Comparison of losartan and hydrochlorothiazide on cognitive function and quality of life in hypertensive patients. Am J Hypertens 1999;12(11 Pt 1):1130-4.
Full Text: Exclude - AD/CD f/u < 1 yr

Teunissen CE, Blom AH, Van Boxtel MP, et al. Homocysteine: a marker for cognitive performance? A longitudinal follow-up study. J Nutr Health Aging 2003;7(3):153-9.
Full Text: Exclude - observational N<300

Teunissen CE, van Boxtel MP, Bosma H, et al. Inflammation markers in relation to cognition in a healthy aging population. J Neuroimmunol 2003;134(1-2):142-50.
Full Text: Exclude - observatioanl N<300

Thomas T, Thomas G, McLendon C, et al. beta-Amyloid-mediated vasoactivity and vascular endothelial damage.[see comment]. Nature 1996;380(6570):168-71.
Full Text: Exclude - risk factor out of scope

Thyrum ET, Blumenthal JA, Madden DJ, et al. Family history of hypertension influences neurobehavioral function in hypertensive patients. Psychosom Med 1995;57(5):496-500.
Full Text: Exclude - risk factor out of scope

Tierney MC, Yao C, Kiss A, et al. Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. Neurology 2005;64(11):1853-9.
Full Text: Exclude - risk factor out of scope

Tilvis RS, Kahonen-Vare MH, Jolkkonen J, et al. Predictors of cognitive decline and mortality of aged people over a 10-year period. J Gerontol A Biol Sci Med Sci 2004;59(3):268-74.
Full Text: Exclude - dementia @ baseline

Tinetti ME, McAvay GJ, Fried TR, et al. Health outcome priorities among competing cardiovascular, fall injury, and medication-related symptom outcomes. J Am Geriatr Soc 2008;56(8):1409-16.
Full Text: Exclude - risk factor out of scope

Toobert DJ, Strycker LA, Glasgow RE, et al. Enhancing support for health behavior change among women at risk for heart disease: the Mediterranean Lifestyle Trial. Health Educ Res 2002;17(5):574-85.
Full Text: Exclude - risk factor out of scope

Toro P, Schonknecht P, Schroder J. Type II diabetes in mild cognitive impairment and Alzheimer's disease: results from a prospective population-based study in Germany. J Alzheimers Dis 2009;16(4):687-91.
Full Text: Exclude - observational N<300

Trompet S, de Craen AJ, Slagboom P, et al. Genetic variation in the interleukin-1 beta-converting enzyme associates with cognitive function. The PROSPER study. Brain 2008;131(Pt 4):1069-77.
Full Text: Exclude - risk factor out of scope

Trompet S, Westendorp RG, Kamper AM, et al. Use of calcium antagonists and cognitive decline in old age. The Leiden 85-plus study. Neurobiol Aging 2008;29(2):306-8.

Full Text: Exclude - observational N<300

Troyer AK, Murphy KJ, Anderson ND, et al. Changing everyday memory behaviour in amnestic mild cognitive impairment: a randomised controlled trial. Neuropsychol Rehabil 2008;18(1):65-88.
Full Text: Exclude - risk factor out of scope

Tsivgoulis G, Alexandrov AV, Wadley VG, et al. Association of higher diastolic blood pressure levels with cognitive impairment. Neurology 2009;73(8):589-95.
Full Text: Exclude - not longitudinal

Tsutsumi T, Don BM, Zaichkowsky LD, et al. Physical fitness and psychological benefits of strength training in community dwelling older adults. Appl Human Sci 1997;16(6):257-66.
Full Text: Exclude - AD/CD f/u < 1 yr

Tucker KL, Qiao N, Scott T, et al. High homocysteine and low B vitamins predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study. Am J Clin Nutr 2005;82(3):627-35.
Full Text: Exclude - observational N<300

Tucker-Drob EM, Johnson KE, Jones RN. The cognitive reserve hypothesis: a longitudinal examination of age-associated declines in reasoning and processing speed. Dev Psychol 2009;45(2):431-46.
Full Text: Exclude - risk factor out of scope

Uusvaara J, Pitkala KH, Tienari PJ, et al. Association between anticholinergic drugs and apolipoprotein E epsilon4 allele and poorer cognitive function in older cardiovascular patients: a cross-sectional study. J Am Geriatr Soc 2009;57(3):427-31.
Full Text: Exclude - risk factor out of scope

van de Rest O, Geleijnse JM, Kok FJ, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. Neurology 2008;71(6):430-8.
Full Text: Exclude - AD/CD f/u < 1 yr

van den Berg E, Biessels GJ, de Craen AJ, et al. The metabolic syndrome is associated with decelerated cognitive decline in the oldest old. Neurology 2007;69(10):979-85.
Full Text: Exclude - observational N<300

van den Berg E, de Craen AJ, Biessels GJ, et al. The impact of diabetes mellitus on cognitive decline in the oldest of the old: a prospective population-based study. Diabetologia 2006;49(9):2015-23.
Full Text: Exclude - obervational N<300

van den Berg E, Dekker JM, Nijpels G, et al. Cognitive functioning in elderly persons with type 2 diabetes and metabolic syndrome: the Hoorn study. Dement Geriatr Cogn Disord 2008;26(3):261-9.
Full Text: Exclude - observational N<300

Van den Heuvel DM, ten Dam VH, de Craen AJ, et al. Increase in periventricular white matter hyperintensities parallels decline in mental processing speed in a non-demented elderly population. J Neurol Neurosurg Psychiatry 2006;77(2):149-53.
Full Text: Exclude - risk factor out of scope

van den Heuvel N, Smits CH, Deeg DJ, et al. Personality: a moderator of the relation between cognitive functioning and depression in adults aged 55-85? J Affect Disord 1996;41(3):229-40.
Full Text: Exclude - not longitudinal

van Dongen MC, van Rossum E, Kessels AG, et al. The efficacy of ginkgo for elderly people with dementia and age-associated memory impairment: new results of a randomized clinical trial. J Am Geriatr Soc 2000;48(10):1183-94.
Full Text: Exclude - dementia @ baseline

van Gelder BM, Tijhuis M, Kalmijn S, et al. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. Am J Clin Nutr 2007;85(4):1142-7.
Full Text: Exclude - observational N<300

van Gelder BM, Tijhuis MA, Kalmijn S, et al. Physical activity in relation to cognitive decline in elderly men: the FINE Study. Neurology 2004;63(12):2316-21.
Full Text: Exclude - observational N<300

van Kooten F, Ciabattoni G, Koudstaal PJ, et al. Increased thromboxane biosynthesis is associated with poststroke dementia. Stroke 1999;30(8):1542-7.
Full Text: Exclude - risk factor out of scope

Van Ness PH, Kasl SV. Religion and cognitive dysfunction in an elderly cohort. J Gerontol B Psychol Sci Soc Sci 2003;58(1):S21-9.
Full Text: Exclude - SPMSQ single test

van Oijen M, Okereke OI, Kang JH, et al. Fasting insulin levels and cognitive decline in older women without diabetes. Neuroepidemiology 2008;30(3):174-9.
Full Text: Exclude - risk factor out of scope

van Swieten JC, Geyskes GG, Derix MM, et al. Hypertension in the elderly is associated with white matter lesions and cognitive decline. Ann Neurol 1991;30(6):825-30.
Full Text: Exclude - observational N<300

van Uffelen JG, Hopman-Rock M, Chin APMJ, et al. Protocol for Project FACT: a randomised controlled trial on the effect of a walking program and vitamin B supplementation on the rate of cognitive decline and psychosocial wellbeing in older adults with mild cognitive impairment [ISRCTN19227688]. BMC Geriatr 2005;5:18.
Full Text: Exclude - methods paper, no primary data

Vanhanen M, Koivisto K, Kuusisto J, et al. Cognitive function in an elderly population with persistent impaired glucose tolerance. Diabetes Care 1998;21(3):398-402.

Full Text: Exclude - not longitudinal

Vanhanen M, Koivisto K, Moilanen L, et al. Association of metabolic syndrome with Alzheimer disease: a population-based study. Neurology 2006;67(5):843-7.
Full Text: Exclude - not longitudinal

Vaughan C, Goldstein FC, Tenover JL. Exogenous testosterone alone or with finasteride does not improve measurements of cognition in healthy older men with low serum testosterone. J Androl 2007;28(6):875-82.
Full Text: Exclude - RCT N<50

Velho S, Marques-Vidal P, Baptista F, et al. Dietary intake adequacy and cognitive function in free-living active elderly: a cross-sectional and short-term prospective study. Clin Nutr 2008;27(1):77-86.
Full Text: Exclude - AD/CD f/u < 1 yr

Vercambre MN, Boutron-Ruault MC, Ritchie K, et al. Long-term association of food and nutrient intakes with cognitive and functional decline: a 13-year follow-up study of elderly French women. Br J Nutr 2009;102(3):419-27.
Full Text: Exclude - not longitudinal

Verhaegen P, Borchelt M, Smith J. Relation between cardiovascular and metabolic disease and cognition in very old age: cross-sectional and longitudinal findings from the berlin aging study. Health Psychol 2003;22(6):559-69.
Full Text: Exclude - observational N<300

Vicario A, Martinez CD, Baretto D, et al. Hypertension and cognitive decline: impact on executive function. J Clin Hypertens (Greenwich) 2005;7(10):598-604.
Full Text: Exclude - observational N<300

Vicini Chilovi B, Conti M, Zanetti M, et al. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. Dement Geriatr Cogn Disord 2009;27(4):390-8.
Full Text: Exclude - observational N<300

Vincze G, Almos P, Boda K, et al. Risk factors of cognitive decline in residential care in Hungary. Int J Geriatr Psychiatry 2007;22(12):1208-16.
Full Text: Exclude - non-Western country

Vinkers DJ, Gussekloo J, Stek ML, et al. Temporal relation between depression and cognitive impairment in old age: prospective population based study. BMJ 2004;329(7471):881.
Full Text: Exclude - Q2 continuous data only

Vinkers DJ, Stek ML, van der Mast RC, et al. Generalized atherosclerosis, cognitive decline, and depressive symptoms in old age. Neurology 2005;65(1):107-12.
Full Text: Exclude - risk factor out of scope

Viramo P, Luukinen H, Koski K, et al. Orthostatic hypotension and cognitive decline in older people. J Am Geriatr Soc 1999;47(5):600-4.
Full Text: Exclude - risk factor out of scope

Viswanath B, Janardhan Reddy YC, Kumar KJ, et al. Cognitive endophenotypes in OCD: a study of unaffected siblings of probands with familial OCD. Prog Neuropsychopharmacol Biol Psychiatry 2009;33(4):610-5.
Full Text: Exclude - risk factor out of scope

Vitaliano PP, Echeverria D, Yi J, et al. Psychophysiological mediators of caregiver stress and differential cognitive decline. Psychol Aging 2005;20(3):402-11.
Full Text: Exclude - dementia @ baseline

Vlad SC, Miller DR, Kowall NW, et al. Protective effects of NSAIDs on the development of Alzheimer disease. Neurology 2008;70(19):1672-7.
Full Text: Exclude - outcomes unacceptably assessed

Vogiatzoglou A, Refsum H, Johnston C, et al. Vitamin B12 status and rate of brain volume loss in community-dwelling elderly. Neurology 2008;71(11):826-32.
Full Text: Exclude - outcomes unacceptably assessed

von Muhlen D, Laughlin GA, Kritz-Silverstein D, et al. The Dehydroepiandrosterone And WellNess (DAWN) study: research design and methods. Contemp Clin Trials 2007;28(2):153-68.
Full Text: Exclude - methods paper, no results

Wadley VG, McClure LA, Howard VJ, et al. Cognitive status, stroke symptom reports, and modifiable risk factors among individuals with no diagnosis of stroke or transient ischemic attack in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Stroke 2007;38(4):1143-7.
Full Text: Exclude - not longitudinal

Wagner S, Kaschel R, Paulsen S, et al. Does a cognitive-training programme improve the performance of middle-aged employees undergoing in-patient psychosomatic treatment? Disabil Rehabil 2008;30(23):1786-93.
Full Text: Exclude - selected population

Waldstein SR, Brown JR, Maier KJ, et al. Diagnosis of hypertension and high blood pressure levels negatively affect cognitive function in older adults. Ann Behav Med 2005;29(3):174-80.
Full Text: Exclude - observational N<300

Waldstein SR, Katzel LI. Gender differences in the relation of hypertension to cognitive function in older adults. Neurol Res 2004;26(5):502-6.
Full Text: Exclude - observational N<300

Waldstein SR, Rice SC, Thayer JF, et al. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. Hypertension 2008;51(1):99-104.
Full Text: Exclude - risk factor out of scope

Wallin MT, Wilken J, Alfaro MH, et al. Neuropsychologic assessment of a population-based sample of Gulf War veterans. Cogn Behav Neurol 2009;22(3):155-66.

Full Text: Exclude - risk factor out of scope

Wang FT, Hu H, Schwartz J, et al. Modifying effects of the HFE polymorphisms on the association between lead burden and cognitive decline. Environ Health Perspect 2007;115(8):1210-5.
Full Text: Exclude - risk factor out of scope

Wang H-X, Karp A, Winblad B, et al. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. Am J Epidemiol 2002;155(12):1081-7.
Full Text: Exclude - <60% of dementia is AD

Wang JY, Zhou DH, Li J, et al. Leisure activity and risk of cognitive impairment: the Chongqing aging study. Neurology 2006;66(6):911-3.
Full Text: Exclude - non-Western country

Wang L, van Belle G, Kukull WB, et al. Predictors of functional change: a longitudinal study of nondemented people aged 65 and older. J Am Geriatr Soc 2002;50(9):1525-34.
Full Text: Exclude - outcomes unacceptably assessed

Wang XM, Fu H, Liu GX, et al. Effect of modified wuzi yanzong granule on patients with mild cognitive impairment from oxidative damage aspect. Chin J Integr Med 2007;13(4):258-63.
Full Text: Exclude - non-Western country

Wardle J, Rogers P, Judd P, et al. Randomized trial of the effects of cholesterol-lowering dietary treatment on psychological function. Am J Med 2000;108(7):547-53.
Full Text: Exclude - AD f/u < 2 yr

Weber P, Meluzinova H, Kubesova H, et al. Insulin treatment in diabetics 75+ years: experiences and results in outpatient care. Adv Gerontol 2008;21(1):143-7.
Full Text: Exclude - comparator is not placebo/control

Weil M, Bressler J, Parsons P, et al. Blood mercury levels and neurobehavioral function. JAMA 2005;293(15):1875-82.
Full Text: Exclude - not longitudinal

Wenisch E, Cantegreil-Kallen I, De Rotrou J, et al. Cognitive stimulation intervention for elders with mild cognitive impairment compared with normal aged subjects: preliminary results. Aging Clin Exp Res 2007;19(4):316-22.
Full Text: Exclude - AD/CD f/u < 1 yr

Weuve J, Korrick SA, Weisskopf MG, et al. Cumulative exposure to lead in relation to cognitive function in older women. Environ Health Perspect 2009;117(4):574-80.
Full Text: Exclude - not longitudinal

Whalley LJ, Deary IJ, Starr JM, et al. n-3 Fatty acid erythrocyte membrane content, APOE varepsilon4, and cognitive variation: an observational follow-up study in late adulthood. Am J Clin Nutr 2008;87(2):449-54.
Full Text: Exclude - observational N<300

Whalley LJ, Fox HC, Deary IJ, et al. Childhood IQ, smoking, and cognitive change from age 11 to 64 years. Addict Behav 2005;30(1):77-88.
Full Text: Exclude - observational N<300

White L, Katzman R, Losonczy K, et al. Association of education with incidence of cognitive impairment in three established populations for epidemiologic studies of the elderly. J Clin Epidemiol 1994;47(4):363-74.
Full Text: Exclude - SPMSQ single test

White LR, Petrovitch H, Ross GW, et al. Brain aging and midlife tofu consumption. J Am Coll Nutr 2000;19(2):242-55.
Full Text: Exclude - not longitudinal

Whitmer RA, Gunderson EP, Quesenberry CP, Jr., et al. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr Alzheimer Res 2007;4(2):103-9.
Full Text: Exclude - not longitudinal

Whitmer RA, Sidney S, Selby J, et al. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005;64(2):277-81.
Full Text: Exclude - outcomes unacceptably assessed

Wilkie FL, Eisdorfer C, Nowlin JB. Memory and blood pressure in the aged. Exp Aging Res 1976;2(1):3-16.
Full Text: Exclude - observational N<300

Williamson JD, Vellas B, Furberg C, et al. Comparison of the design differences between the Ginkgo Evaluation of Memory study and the GuidAge study. J Nutr Health Aging 2008;12(1):73S-9S.
Full Text: Exclude - methods - no data

Wilson RS, Arnold SE, Schneider JA, et al. Chronic distress, age-related neuropathology, and late-life dementia. Psychosom Med 2007;69(1):47-53.
Full Text: Exclude - observational N<300

Wilson RS, Barnes LL, Bennett DA, et al. Proneness to psychological distress and risk of Alzheimer disease in a biracial community. Neurology 2005;64(2):380-2.
Full Text: Exclude - risk factor out of scope

Wilson RS, Mendes De Leon CF, Bennett DA, et al. Depressive symptoms and cognitive decline in a community population of older persons. J Neurol Neurosurg Psychiatry 2004;75(1):126-9.
Full Text: Exclude - Q2 continuous data only

Wolf PA, Beiser A, Elias MF, et al. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. Curr Alzheimer Res 2007;4(2):111-6.
Full Text: Exclude - not longitudinal

Wolfson C, Perrault A, Moride Y, et al. A case-control analysis of nonsteroidal anti-inflammatory drugs and Alzheimer's disease: are they protective? Neuroepidemiology 2002;21(2):81-6.
Full Text: Exclude - AD f/u < 2 yr

Wolinsky FD, Unverzagt FW, Smith DM, et al. The ACTIVE cognitive training trial and health-related quality of life: protection that lasts for 5 years. J Gerontol A Biol Sci Med Sci 2006;61(12):1324-9.
Full Text: Exclude - no cognitive end points

Wolkowitz OM, Kramer JH, Reus VI, et al. DHEA treatment of Alzheimer's disease: a randomized, double-blind, placebo-controlled study. Neurology 2003;60(7):1071-6.
Full Text: Exclude - dementia @ baseline

Wolozin B, Kellman W, Ruosseau P, et al. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol 2000;57(10):1439-43.
Full Text: Exclude - not longitudinal

Wolters M, Hickstein M, Flintermann A, et al. Cognitive performance in relation to vitamin status in healthy elderly German women-the effect of 6-month multivitamin supplementation. Prev Med 2005;41(1):253-9.
Full Text: Exclude - AD/CD f/u < 1 yr

Woo J, Lau E, Ho SC, et al. Comparison of Pueraria lobata with hormone replacement therapy in treating the adverse health consequences of menopause. Menopause 2003;10(4):352-61.
Full Text: Exclude - AD/CD f/u < 1 yr

Woo J, Lynn H, Lau WY, et al. Nutrient intake and psychological health in an elderly Chinese population. Int J Geriatr Psychiatry 2006;21(11):1036-43.
Full Text: Exclude - AD f/u < 2 yr

Woods NF, Carr MC, Tao EY, et al. Increased urinary cortisol levels during the menopausal transition. Menopause 2006;13(2):212-21.
Full Text: Exclude - risk factor out of scope

Worth RM, Kagan A. Ascertainment of men of Japanese ancestry in Hawaii through World War II Selective Service registration. J Chronic Dis 1970;23(5):389-97.
Full Text: Exclude - risk factor out of scope

Wright CE, Kunz-Ebrecht SR, Iliffe S, et al. Physiological correlates of cognitive functioning in an elderly population. Psychoneuroendocrinology 2005;30(9):826-38.
Full Text: Exclude - AD f/u < 2 yr

Wroolie TE, Kenna HA, Williams KE, et al. Cognitive effects of memantine in postmenopausal women at risk of dementia: a pilot study. Acta Neurol Scand 2009;119(3):172-9.
Full Text: Exclude - AD/CD f/u < 1 yr

Wu JH, Haan MN, Liang J, et al. Impact of antidiabetic medications on physical and cognitive functioning of older Mexican Americans with diabetes mellitus: a population-based cohort study. Ann Epidemiol 2003;13(5):369-76.
Full Text: Exclude - risk factor out of scope

Wu YH, Feenstra MG, Zhou JN, et al. Molecular changes underlying reduced pineal melatonin levels in Alzheimer disease: alterations in preclinical and clinical stages. J Clin Endocrinol Metab 2003;88(12):5898-906.
Full Text: Exclude - risk factor out of scope

Wurzelmann J, Frishman WH, Aronson M, et al. Neuropsychological effects of antihypertensive drugs. Cardiol Clin 1987;5(4):689-701.
Full Text: Exclude - not longitudinal

Xiong GL, Plassman BL, Helms MJ, et al. Vascular risk factors and cognitive decline among elderly male twins. Neurology 2006;67(9):1586-91.
Full Text: Exclude - <60% of dementia is AD

Xu G, Liu X, Yin Q, et al. Alcohol consumption and transition of mild cognitive impairment to dementia. Psychiatry Clin Neurosci 2009;63(1):43-9.
Full Text: Exclude - non-Western country

Xu W, Qiu C, Winblad B, et al. The effect of borderline diabetes on the risk of dementia and Alzheimer's disease. Diabetes 2007;56(1):211-6.
Full Text: Exclude - risk factor out of scope

Yaffe K, Barnes D, Lindquist K, et al. Endogenous sex hormone levels and risk of cognitive decline in an older biracial cohort. Neurobiol Aging 2007;28(2):171-8.
Full Text: Exclude - risk factor out of scope

Yaffe K, Barrett Connor E, Lin F, et al. Serum lipoprotein levels, statin use, and cognitive function in older women. Arch Neurol 2002;59(3):378-84.
Full Text: Exclude - not longitudinal

Yaffe K, Ettinger B, Pressman A, et al. Neuropsychiatric function and dehydroepiandrosterone sulfate in elderly women: a prospective study. Biol Psychiatry 1998;43(9):694-700.
Full Text: Exclude - risk factor out of scope

Yaffe K, Lindquist K, Shlipak MG, et al. Cystatin C as a marker of cognitive function in elders: findings from the health ABC study. Ann Neurol 2008;63(6):798-802.
Full Text: Exclude - risk factor out of scope

Yaffe K, Lui LY, Grady D, et al. Cognitive decline in women in relation to non-protein-bound oestradiol concentrations. Lancet 2000;356(9231):708-12.
Full Text: Exclude - risk factor out of scope

Yamada M, Kasagi F, Sasaki H, et al. Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. J Am Geriatr Soc

2003;51(3):410-4.
Full Text: Exclude - not general population

Yamada M, Mimori Y, Kasagi F, et al. Incidence and risks of dementia in Japanese women: Radiation Effects Research Foundation Adult Health Study. J Neurol Sci 2009;283(1-2):57-61.
Full Text: Exclude - not general population

Yen PK. Maintaining cognitive function with diet. Geriatr Nurs 2003;24(1):62-3.
Full Text: Exclude - risk factor out of scope

Yip AG, Brayne C, Matthews FE. Risk factors for incident dementia in England and Wales: The Medical Research Council Cognitive Function and Ageing Study. A population-based nested case-control study. Age Ageing 2006;35(2):154-60.
Full Text: Exclude - <60% of dementia is AD

Yip AG, Green RC, Huyck M, et al. Nonsteroidal anti-inflammatory drug use and Alzheimer's disease risk: the MIRAGE Study. BMC Geriatr 2005;5:2.
Full Text: Exclude - dementia @ baseline

Yodfat Y, Bar-On D, Amir M, et al. Quality of life in normotensives compared to hypertensive men treated with isradipine or methyldopa as monotherapy or in combination with captopril: the LOMIR-MCT-IL study. J Hum Hypertens 1996;10(2):117-22.
Full Text: Exclude - comparator not placebo/control

Young SE, Mainous AG, 3rd, Carnemolla M. Hyperinsulinemia and cognitive decline in a middle-aged cohort. Diabetes Care 2006;29(12):2688-93.
Full Text: Exclude - risk factor out of scope

Zamrini E, McGwin G, Roseman JM. Association between statin use and Alzheimer's disease. Neuroepidemiology 2004;23(1-2):94-8.
Full Text: Exclude - outcome non-specific AD

Zhang Z, Gu D, Hayward MD. Early life influences on cognitive impairment among oldest old Chinese. J Gerontol B Psychol Sci Soc Sci 2008;63(1):S25-33.
Full Text: Exclude - non-Western country

Zhang ZX, Plassman BL, Xu Q, et al. Lifespan influences on mid- to late-life cognitive function in a Chinese birth cohort. Neurology 2009;73(3):186-94.
Full Text: Exclude - non-Western country

Zielinska J, Ryglewicz D, Wierzchowska E, et al. Anticardiolipin antibodies are an independent risk factor for ischemic stroke. Neurol Res 1999;21(7):653-7.
Full Text: Exclude - risk factor out of scope

Zimpfer D, Czerny M, Vogt F, et al. Neurocognitive deficit following coronary artery bypass grafting: a prospective study of surgical patients and nonsurgical controls. Ann Thorac Surg 2004;78(2):513-8; discussion 518-9.
Full Text: Exclude - risk factor out of scope

Zunzunegui MV, Beland F, Gutierrez-Cuadra P. Loss to follow-up in a longitudinal study on aging in Spain. J Clin Epidemiol 2001;54(5):501-10.
Full Text: Exclude - risk factor out of scope