Technical Report

Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: A Decision Analysis

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Structured Abstract

Background: Evidence indicates that aspirin is effective for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC), but regular use also increases risk for gastrointestinal (GI) and cerebral hemorrhages.

Objective: To assess the net balance of benefits and harms from routine use of aspirin for primary prevention across clinically relevant age, sex, and CVD risk groups.

Design: Decision analysis using a microsimulation model.

Data Sources: Relative risks of aspirin benefits and harms are sourced from three updated systematic evidence reviews.

Target Population: Men and women aged 40 to 79 years with 10-year CVD risk of 20 percent or less, no history of CVD, and non-elevated risk for GI or cerebral hemorrhage.

Time Horizon: Lifetime, 20 years, and 10 years.

Perspective: Clinical.

Intervention: Daily use of low-dose aspirin (100mg or less).

Outcome Measures: Primary outcomes are net benefits in terms of life years and quality-adjusted life years (QALYs). Benefits include reduction of non-fatal myocardial infarction, non-fatal ischemic stroke, fatal CVD, CRC incidence, and CRC mortality. Harms include increase in fatal and non-fatal GI bleeding and hemorrhagic stroke.

Results of Base-Case Analysis: Lifetime net benefits from routine aspirin use for primary prevention are found to be positive for men and women aged 40-69 in all 10-year CVD risk levels. For men and women aged 70-79, lifetime net outcomes are mixed: net life years are negative, but net QALYs are positive. The largest lifetime net benefits from aspirin are found among men and women aged 40-59 with moderate-to-high baseline CVD risk. Net benefits from aspirin over 10 and 20 years of use are generally much lower and may be negative. Net benefit calculations also favor early over delayed initiation of aspirin use for all men and women aged 40-69.

Results of Sensitivity Analysis: Net benefit results are most sensitive to uncertainty regarding the effect of low-dose aspirin on the increased risk of hemorrhagic stroke and in the primary prevention of CVD mortality. Imposing small disutilities on routine aspirin use can substantially diminish the net benefit of using aspirin to improve overall quality of life.

Limitations: Sensitivity analyses demonstrate that our current imprecision in understanding aspirin's effects on benefits and harms, when used for primary prevention, carry through to model estimates. Persons aged 40-49 are not as well represented in the studies informing aspirin's effects, and therefore, the modeling results may not reliably apply to persons in this age

group. Improved ability to estimate individual GI bleeding risk would enhance precision. Modeled results do not account for potential correlations between CVD risk factors and GI bleeding risk, except for age and sex.

Conclusion: Benefits are predicted to exceed harms among persons aged 40-69 with non-elevated bleeding risk who take aspirin for primary prevention of CVD and CRC over their lifetimes. Net benefits from routine aspirin use over a 10- or 20-year horizon are expected to be substantially smaller, and in many cases, harms may exceed benefits. Findings do not differ markedly between men and women; however, deterministic and probabilistic sensitivity analyses reveal meaningful uncertainty about the magnitude of net benefit.

Chapter 1. Introduction

Cardiovascular disease (CVD) and cancer are the leading causes of deaths in the United States, and combined, the diseases accounted for more than half of all mortality in 2010.[1] In any given year, approximately 635,000 Americans will suffer their first coronary attack, 610,000 will suffer their first stroke, and one-third of all cardiovascular deaths will occur among persons younger than 75 years old.[2] Among cancers, colorectal cancer (CRC) is the third most common and deadly, accounting for about 8 percent of all new cases and deaths.[3] In economic terms, CVD and CRC account for more than $200 billion in direct medical costs annually, and the indirect costs from lost productivity and premature mortality are estimated to exceed at least another $100 billion.[2,4,5]

Evidence for the effectiveness in preventing recurrent complications from heart disease and stroke is believed to be strong,[6,7] but the evidence for aspirin's net benefit in preventing CVD and cancers, including CRC, in healthy individuals has been more mixed.[7-12] Three recent systematic reviews conducted on behalf of the United States Preventive Services Task Force (USPSTF) investigated the current evidence for the benefits and harms of aspirin in the primary prevention of CVD, all-cause mortality, all cancers, and CRC.[13-15] These reviews identified evidence of aspirin's effectiveness in preventing first-time myocardial infarction and ischemic stroke—now for both men and women—and found new evidence indicating aspirin's effectiveness in preventing CRC. However, the updated reviews also reaffirm aspirin's role in increasing risk for major gastrointestinal (GI) bleeding and hemorrhagic stroke.

The central clinical dilemma faced when deciding whether aspirin is appropriate for the primary prevention of CVD and CRC is an uncertain relationship between the benefits and harms of long-term aspirin use. The reductions in relative risk are sizable, but in comparison with secondary prevention, the number of treated persons needed to prevent a single first event are relatively large. The objective of this study is to conduct a decision analysis using simulation modeling to better inform clinical guidance by assessing the expected net benefit of aspirin use for primary prevention across clinically relevant population groups defined by their age, sex, and underlying CVD risk characteristics. The results of this study are intended to support a USPSTF review—and possible update—of the 2009 recommendation on aspirin use.[9]

Chapter 2. Methods

This decision analysis uses microsimulation modeling to assess the net balance of harms and benefits from routine use of aspirin for the primary prevention of CVD and CRC using evidence from the corresponding recent systematic evidence reviews conducted for the USPSTF.[13-15] Net benefits are independently assessed across three dimensions (sex, age, and baseline 10-year CVD risk) and three time horizons (lifetime, 20 years, and 10 years). Our only decision analytic measure is whether net benefit is positive or negative (i.e., indicating net harm). Decision makers may weigh the size of expected net benefit against uncertainty of the estimates to determine appropriateness of aspirin use.

Key Questions

The decision model addressed the following key questions:

1a. What is the **lifetime net benefit**, in terms of life years and quality-adjusted life years, of routine aspirin use at a minimally effective dose for CVD prevention by sex and 10-year age group?
1b. What is the **net benefit over 20 years**, in terms of life years and quality-adjusted life years, of routine aspirin use at a minimally effective dose for CVD prevention by sex and 10-year age group?
1c. What is the **net benefit over 10 years**, in terms of life years and quality-adjusted life years, of routine aspirin use at a minimally effective dose for CVD prevention by sex and 10-year age group?
2. What is the **marginal lifetime net benefit**, in terms of life years and quality-adjusted life years, of initiating aspirin for chemoprevention **now versus 10 years from now** by sex and 10-year age group?

Model Design

Analyses in this study were conducted using the HealthPartners Institute for Education and Research ModelHealth™: Cardiovascular disease microsimulation model. This model was originally designed to assess value of the current USPSTF aspirin counseling and CVD screening recommendations for the National Commission on Prevention Priorities. We added a CRC module capable of assessing primary prevention of either CRC cases or deaths directly. We also incorporated detailed tobacco use microsimulation functions from the HealthPartners Institute for Education and Research ModelHealth™: Tobacco model to capture correlation of smoking risk between CVD and CRC at the level of individual patients. Appendix B provides a detailed description of the microsimulation model used for this study.

ModelHealth: CVD is a Markov-based, annual-cycle microsimulation model parameterized to estimate the lifetime incidence of CVD events in a cross-section of individuals representative of the U.S. population. Modeled outcomes include incidence of myocardial infarction, ischemic

stroke, hemorrhagic stroke, angina pectoris, congestive heart failure, intermittent claudication, diabetes, and CVD-related death. Demographically, variations in age, sex, and race/ethnicity are accounted for in the baseline prevalence of disease and in the distribution and progression of CVD risk factors. These include an individual's body mass index (BMI), systolic blood pressure (SBP), high- and low-density lipoprotein cholesterol (HDL-C/LDL-C), and cigarette smoking status.

CVD incidence is modeled annually. Events are predicted by one-year risk equations estimated specifically for the model from long-term epidemiological data sourced from the Framingham Heart Study.[16,17] Event risk is estimated based on a person's age, sex, BMI, blood pressure, cholesterol levels, smoking status, and previous history of CVD. Disease risk is not adjusted by race/ethnicity, but recent evidence suggests that there may not be independent risk of CVD associated with race and ethnicity, once demographic differences in CVD risk factors have been taken into account.[18,19]

CRC is modeled using an incidence and case-fatality rate approach, which tracks cancer incidence and mortality for each agent. Baseline incidence and case-fatality rates by age, sex, and race/ethnicity are estimated from National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data using SEER*Stat software.[20] Baseline incidence and case-fatality rates are further adjusted according to smoking status using relative risks provided by the Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) tool maintained by the Centers for Disease Control and Prevention.[21]

The annual progression of continuous CVD risk factors is modeled in a two-step process. First, the probability of an increase, decrease, or maintenance of a risk factor is determined given individual characteristics and the previous year's value. Second, if a risk factor changes, the amount of change is determined by a second set of equations using the same covariates. We estimated the equations that determine these probabilities using the Behavioral Risk Factor Surveillance System[22] and the Framingham Heart Study data.[16,17] Tobacco initiation and cessation depend on a person's current smoking status, time in that state, and their demographic characteristics using probabilities derived from the National Health Interview Survey data[23] and published estimates from longitudinal studies.[24,25] Projected changes in future smoking behavior have been calibrated to Congressional Budget Office estimates.[26]

Screening and treatment for hypertension and dyslipidemia in the model are consistent with national clinical guidelines,[27,28] and identification and adherence patterns are consistent with the rates observed within the National Health and Nutrition Examination Survey (NHANES).[29-33] The use of antihypertensive drugs and lipid-acting agents is modeled as an exogenous treatment effect on top of the estimated natural progression of these respective risk factors and alters disease risk accordingly. The use of aspirin may affect the relative risk of non-fatal myocardial infarction and ischemic stroke, CVD-related mortality, CRC incidence, major GI bleeding, and hemorrhagic stroke.

Baseline Event Rates and Model Validation

Baseline rates of CVD events are generated by the combination of population characteristics at model initiation, the model's estimation of the natural progression of CVD risk factors as individuals age, and the model's risk equations for disease. Appendix A contains additional tables and figures. **Appendix A Table 1** presents prevalence rates of myocardial infarction and ischemic stroke generated by the model for a birth cohort starting at age 40 and compares these values to corresponding rates observed in NHANES[29-33] as a benchmark for the external validity of the ModelHealth: CVD natural history engine. Baseline rates of major GI bleeding in the non-elevated risk population (e.g., excluding persons with prior bleeding history or other contraindications) were estimated using data from a large Italian population-based cohort study,[34] with adjustments made for the U.S. age and sex distribution (**Table 1**). GI bleed case-fatality rates, based on patients without complicating comorbidities, were derived from a 74-hospital prospective study in the United Kingdom.[35] Baseline CRC incidence rates used in the model reflect contemporary use of screening technologies, such as colonoscopy, which can prevent CRC by the identification and removal of precursor adenomatous polyps or adenoma.

Integration of Systematic Review Results Into the Model

Findings from the three coordinated systematic evidence reviews on aspirin conducted on behalf of the USPSTF were integral to the parameter assumptions and model design in this study.[13-15] These reviews incorporated the latest evidence on aspirin's potential benefits and harms in the primary prevention of CVD, CRC, and all cancers combined. The reviews found evidence that daily aspirin use reduces the risk of non-fatal myocardial infarction, non-fatal stroke, and, after 10 years of use, CRC incidence and mortality. Aspirin also was found to increase the risk of fatal and non-fatal hemorrhagic stroke and major GI bleeding. The best balance of cardiovascular benefits to harms was reflected in daily aspirin doses of 100mg or less. Benefits with respect to CRC incidence were not strongly correlated with dose. There was not clear or compelling evidence that aspirin changes the relative risk of CVD death or fatal GI bleeds. Nor was there evidence that aspirin effects are differential by age or, in contrast to prior findings from the prior USPSTF review,[9,36] by sex. Evidence review findings also were used to inform baseline levels of GI bleeding risk and the selection of the American College of Cardiology and American Heart Association (ACC/AHA) risk calculator to determine baseline CVD risk in the model.[37] The systematic reviews did not assess the evidence for aspirin use in secondary prevention of CVD.

Aspirin Benefits and Harms

All aspirin effects were modeled as relative risk modifications to the annual probability of an event. Model parameters for primary prevention are summarized in **Table 1**. CVD and bleeding relative risks were derived from seven low-dose primary prevention trials, defined as 100mg of aspirin per day or less, identified by the systematic evidence review.[13,38-44] The effect of aspirin on the relative risk of developing colorectal cancer was estimated from three randomized clinical trials identified by the systematic evidence review,[14,45,46] but is restricted to a benefit observed after 10 years of continuous use. All non-CRC benefits and harms are assumed to take effect immediately, and all relative risks are assumed to return to 1.00 with discontinuation of aspirin.

Indirect effects of aspirin on CVD incidence and mortality may arise when the prevention or occurrence of an initial event alters the disease progression probabilities for subsequent events, as determined by the Framingham-derived risk equations internal to the model (**Appendix B Table 3**). Effects of aspirin after experiencing a non-fatal CVD event are derived from secondary prevention trials (**Appendix B Table 6**).

Quality-of-Life Weights

Health utilities for the major outcomes affected by aspirin use were estimated using literature sources[47-53] and are summarized in **Table 2**. Living without a CVD condition or CRC was given a health utility of 0.872. All other health utility weights were applied multiplicatively to that baseline. Disutilities from myocardial infarction and GI bleeding events were applied only during the year an event occurs. In the base-case analysis, no disutility was applied to taking aspirin daily, but two alternative scenarios with aspirin disutilities included were considered in sensitivity analysis. Quality-of-life reductions for congestive heart failure were included because, as a major sequela to myocardial infarction, incidence may be indirectly affected by aspirin use in the model.

Patient Population

The key questions were assessed independently for men and women across four 10-year age bands (40-49, 50-59, 60-69, and 70-79 years old) and across baseline 10-year CVD risk bands ranging from 1-20%. Baseline 10-year CVD risk was rounded to the nearest integer and estimated using the ACC/AHA risk calculator for the first hard atherosclerotic cardiovascular disease (ASCVD) event (non-fatal MI, non-fatal stroke, or coronary death).[37] The calculation of CVD risk at baseline is independent from the event rates predicted by the model and mirrors CVD risk identification as it may be practiced in clinical settings. For each age, sex, and baseline CVD risk band, simulated persons were randomly oversampled from population characteristics representative of the U.S. population. For men aged 60-79 and women aged 70-79, low 10-year risk bands that are rarely or never observed were excluded. To define the representative U.S. population, initial demographic characteristics—including age, sex, and race/ethnicity—were drawn from the United States Census.[54] Initial CVD risk factors, including BMI, SBP, LDL, HDL, and diabetes status, were derived from the combined 2001-2010 NHANES surveys.[29-33] Initial smoking status is derived from the 2007 National Health Interview Survey[23] and calibrated to estimates by the Congressional Budget Office.[26] All persons for the decision analysis were assumed to be free of CVD and CRC at baseline. **Table 3** illustrates how the ACC/AHA risk bands are distributed across the U.S. population.

Base-Case Analysis

All analyses compared outcomes of a simulated population routinely using aspirin for the primary prevention of CVD (i.e., prior to any major events) to the same population, all else held equal, not using aspirin for primary prevention. For secondary prevention (e.g., after a major CVD event), aspirin was initiated at contemporary rates of adherence (**Appendix B Table 11**) in both simulation arms. To align with common clinical practice, aspirin use was discontinued

permanently in both arms after any major GI bleeding or hemorrhagic stroke event. Life years and quality-adjusted life years (QALYs) were the primary outcomes of interest, but all modeled benefit and harm events also were measured. Decision analysis criteria were limited to an assessment of positive or negative net balance of life years, QALYs, and event counts. Model simulations were independently conducted with a sample population of 100,000 persons for each age, sex, and baseline CVD risk group.

Uncertainty and Sensitivity Analysis

Two sources of uncertainty were considered in this study: stochastic heterogeneity resulting from the variability in outcomes experienced by a randomly selected sample population and parameter uncertainty resulting from the imprecision of model parameter estimates.[55] Confidence intervals reflecting stochastic heterogeneity were estimated by bootstrap resampling the simulated population for each stratified outcome 100,000 times with replacement.

Deterministic (one-way) sensitivity analyses of key parameters were conducted by replicating simulations with all other parameters, probabilities, and population characteristics held equal. Monte Carlo methods were used to perform probabilistic sensitivity analyses, with parameter values approximated using a triangle distribution. **Table 1** presents the parameter value ranges used in the deterministic and probabilistic sensitivity analyses. Uncertainty in aspirin's effect to reduce CVD mortality risk was included among the sensitivity analysis parameters because a small but not statistically significant effect was observed in the systematic review. Parameter values for the relative risk of CVD mortality and hemorrhagic stroke were capped at 1.00 to maintain consistency in the directionality of aspirin benefits and harms.

Chapter 3. Results

KQ 1a. What Is the Lifetime Net Benefit of Aspirin?

In the base-case analyses, the predicted lifetime net benefit from the routine use of aspirin for primary prevention of CVD and CRC is positive in terms of QALYs for all considered age, sex, and baseline CVD risk groups (**Table 4**). In terms of life years, the lifetime net benefit is found to be positive for all groups aged 40-69, but negative for all groups aged 70-79. Nearly all these results are statistically different from zero when accounting for stochastic heterogeneity reflected in the confidence intervals also presented in **Table 4**. The exception is when considering the life years measure for men and women aged 60-69 at 5% baseline CVD risk and lower. The magnitude of lifetime net benefit is generally similar between men and women, with the exception of a sizable (1.5 times or greater) difference in net life years for men compared with women at very low (1%) baseline CVD risk from aged 40-59. This is likely due to the larger proportion of young, low-risk men who eventually face high CVD risk in older age in comparison to women. These patterns hold essentially the same when the outcomes are discounted to present value at 3% per year (**Appendix A Table 2**).

Detailed appendix tables present outcomes in terms of net prevented events, net harm events, and net total events prevented (**Appendix A Tables 5-12**). Differences in baseline incidence for myocardial infarction (higher for men), ischemic stroke (higher for women), and GI bleeding (higher for women) account for differences in lifetime net incidence by sex. Women also have a longer life expectancy, which corresponds to a longer average risk exposure during which aspirin can intervene.

When comparing by age groups, the net lifetime CVD events and CRC cases prevented are lowest at older ages. This corresponds with the decline in person-years of risk exposure. Conversely, on the other side of the ledger, increases in baseline GI bleeding and hemorrhagic stroke risk with age are sufficient to keep net lifetime harms similar among age groups. One notable exception is a higher rate of net GI bleed deaths for persons aged 70-79 years. This is attributable to the large jump in case-fatality rates for this age group. Combined, lifetime net events prevented are highest for ages 40-49 and lowest for ages 70-79. Lifetime net events prevented are positive for all evaluated groups of men and women aged 40-69, but are negative for all evaluated baseline CVD risk ranges of men aged 70-79 and for baseline CVD risk of 10% and lower of women aged 70-79. Net events prevented generally correlate with net life years and net QALYs. However, as seen among men and women aged 70-79, net life years can be negative while net QALYs are positive. Timing is important in such cases, when early benefits primarily involve the prevention of non-fatal events and early harms are relatively more likely to be fatal.

KQ 1b. What Is the Net Benefit of Aspirin Over 20 Years?

Over 20 years, the predicted net benefit from aspirin in terms of QALYs remains positive for all evaluated age, sex, and baseline CVD risk groups (**Table 5**). However, the magnitude of net benefit over 20 years is generally a small fraction of the lifetime net benefit. For example, for

men and women aged 40-49, the magnitude of net benefit over 20 years is less than one-sixth the lifetime net benefit, and for most cases, the magnitude of 20-year net benefit is less than half the lifetime net benefit. In terms of life years, most cases indicate a shift from positive net benefit over a lifetime to net harm over 20 years. Men and women aged 40-59 at 10% baseline CVD risk and greater are an exception. Most of these population groups have only marginally positive net benefit, and many cases are not statistically different from zero when stochastic heterogeneity is taken into account. These patterns generally hold when the outcomes are discounted to present value (**Appendix A Table 3**) and when detailed outcomes are considered (**Appendix A Tables 5-12**). Net events prevented are generally found to remain positive over the 20-year horizon—with an exception of among men aged 70-79—including many cases in which net life years are negative.

KQ 1c. What Is the Net Benefit of Aspirin Over 10 Years?

Over 10 years, the net benefit of aspirin is generally found to be negative or only marginally positive for all evaluated age, sex, and baseline CVD risk groups (**Table 6**). Due to its assumed delayed effect, no CRC benefit is reflected in 10-year results. In terms of life years, net benefit is not found to be positive for any cases during the first 10 years. In terms of QALYs, small positive mean net benefits are found for men and women at incrementing risk thresholds by age group—e.g., at 1% baseline CVD risk for women aged 40-49 and at 20% risk for women aged 70-79. Although the incidence of events that may be prevented by aspirin is higher in older age groups, the risk of harms—GI bleeding, in particular—also increases considerably with age. These observed patterns show no meaningful difference when discounting to present value (**Appendix A Table 4**). Most patterns follow as expected for the net event rates over 10 years (**Appendix A Tables 5-12**).

KQ 2. What Is the Marginal Net Benefit of Initiating Aspirin Now Versus Waiting 10 Years?

The results from KQ1a-c do not directly indicate whether similar lifetime net benefits could be achieved when waiting to initiate routine aspirin use in younger persons. **Table 7** describes the marginal lifetime net benefits expected from an immediate initiation of aspirin in comparison to a 10-year delay for men and women from 40-69 years. In all cases, the net benefits of earlier initiation in terms of life years and QALYs are found to be positive, and all stochastic heterogeneity confidence intervals are positive as well. The magnitude of net benefit is generally monotonically increasing by baseline CVD risk, with marginal net benefit approximately 2-4 times greater between the 1% and 20% baseline CVD risk groups. Similar results are observed when outcomes are discounted to present value (**Appendix A Table 16**).

Deterministic (One-Way) Sensitivity Analyses (KQs 1a–c)

General sensitivity in the net benefit estimates to specific parameter assumptions is demonstrated graphically in **Figure 1** by averaging lifetime outcomes across all age, sex, and baseline CVD

risk groups. The figure shows that the possibility for a direct reduction in the relative risk of CVD-related death from aspirin (cases 6 and 7) has by far the most potential to sway results, measured in both life years and QALYs. The next most sensitive parameter to both measures is the relative risk for hemorrhagic stroke due to aspirin use (cases 13 and 14). Some parameter assumptions have differential sensitivity on the two main outcome measures. For example, adding a small disutility from the routine use of aspirin (cases 1 and 2) can have sizable impact on net quality of life estimates, but has no effect on life years. In addition, a greater sensitivity to QALYs compared to life years can be seen for aspirin's effect on the relative risk of ischemic stroke (cases 15 and 16). The relativity and scale in parameter sensitivity can also be seen in the scatter plot presented in **Appendix A Figure 1**.

Appendix A Table 13 compares the one-way parameter sensitivity in lifetime net benefit for men and women at 10% baseline CVD risk. Notably, adding even a small 0.005 quality-of-life disutility associated with routine aspirin use (case 1) dramatically shifts QALY results. With that modeling change, net QALYs per 1,000 men and women aged 50-59 fall to -3.2 and 0.8, respectively, from the base case values of 75.1 and 88.5. The CRC incidence reduction benefit from aspirin is shown to be an important one; if this benefit did not exist (case 3), QALY net benefits would fall by roughly 50 percent and life year net benefits would fall by even more. Case 7 illustrates that the inclusion of a 4 percent reduction in relative risk for CVD-related death from aspirin nearly doubles the life year and QALY impact for men and women aged 40-49, increases net benefit by about five-fold for these measures for men and women in their 60s, and results in positive net benefits for people in their 70s.

Sensitivity to the relative risk of GI bleeding incidence with aspirin, the case-fatality rate from GI bleeds, and the population-wide baseline risk for GI bleeding (cases 8-12) is moderate and proportional. Similarly, sensitivity in the hemorrhagic and ischemic stroke and myocardial infarction relative risk parameters (cases 13-18) is moderate and approximately proportional to the shift in the parameter values from their baseline assumptions.

Similar sensitivity patterns, to a smaller scale, can be seen in **Appendix A Tables 14** and **15** for the 20- and 10-year horizons, respectively. One notable exception is that the CRC parameter has no effect on the 10-year results, consistent with the results of the systematic review.

Probabilistic Sensitivity Analyses (KQs 1a–c)

Mean results from the probabilistic parameter sensitivity analyses (**Table 8**) are all positive and higher than the mean values found in the base case analyses because of the inclusion of sensitivity around the assumption of an effect of aspirin on the relative risk of CVD death, which was bounded to be 1.0 or lower. Due to this bound, the average relative risk for CVD is less than 1.0 in these sensitivity analyses, whereas it was set equal to 1.0 in the base case. This difference increases with age, as the probability of CVD death increases. Despite the inclusion of this additional benefit in the average, the confidence intervals of many of the net benefit outcomes include zero. This indicates that a meaningful proportion of cases where parameter values are in the low confidence range of benefits, or the high confidence range of harms, lead to findings of aspirin use causing net harm. Exceptions where the confidence intervals do not include zero are

the lifetime net life years for men and women aged 40-59 years, lifetime net QALYs for men aged 40-59 and women aged 40-69, and 20-year and 10-year net QALYs for women aged 40-59.

Chapter 4. Discussion

These estimates quantify the expected net benefit from taking daily low-dose aspirin for the primary prevention of CVD and CRC by age, sex, and baseline 10-year CVD risk group, as derived from a detailed microsimulation model. To assist decision-making, we provide these estimates for a lifetime analytic horizon, as well as over 10 and 20 years for additional context. We also approximate the marginal benefit of immediate versus 10-year delayed initiation of aspirin for different age groups.

Overall, we find that the net lifetime benefits from taking aspirin are predicted to be positive in terms of net life years, QALYs, and events for men and women of all 10-year CVD risk levels aged 40-69. For most men aged 70-79 in the 10-year CVD risk ranges we considered, expected net life years and net events are negative and net QALYs are positive from a lifetime perspective. For women aged 70-79, lifetime net benefits from aspirin are similarly mixed: expected net life years are negative, net QALYs are positive, and net events are positive for women with 10-year CVD risk of 10% and greater. Twenty-year net benefits for men and women aged 40-69 are generally much smaller and sometimes negative, and 10-year net benefits are generally only marginally positive or negative. For all men and women aged 40-69, our analysis favors early versus delayed initiation of aspirin use. Although our analysis only addressed populations with baseline 10-year CVD risk of 20 percent or less, results for populations with higher risk are expected to be monotonically consistent.

Comparison to 2009 USPSTF Findings

The evidence findings informing our analysis diverge from those informing the 2009 USPSTF aspirin recommendation in several important ways. The most apparent difference is that the updated evidence review no longer finds a difference in benefits between men and women. Previously, aspirin was found to reduce the relative risk of MI in men by 32% and stroke in women by 17%; the updated review finds that aspirin reduces the relative risk of MI and stroke in both men and women by 15% and 18%, respectively. That difference means larger expected benefits for women, but the contrast is less clear for men, because MIs are more prevalent than strokes but strokes tend to have greater impact on quality of life and risk of death. Previous findings applied to men aged 45-79 and women aged 55-79, but the updated reviews considered evidence for men and women aged 40 and older. Another major difference is the new finding of lower CRC incidence risk after 10 years of aspirin use. This added benefit can account for more than half of the lifetime net benefit, in terms of life years and QALYs, from routine aspirin use (**Appendix A Table 13**, **Case 3**). Finally, the findings on harms associated with routine aspirin use also have been updated. The prior estimated rate of excess GI bleeds due to aspirin reflected a relative risk of 2.00, compared to 1.59 in the updated review. This results in approximately 40 percent fewer estimated excess GI bleeding events in our analysis. The relative risk of hemorrhagic stroke with aspirin was previously found to be 1.69, but the current best estimate is substantially lower at a relative risk of 1.14.

There are also numerous methodological differences in our approach to estimating net benefit compared to the calculations that informed the 2009 USPSTF aspirin recommendation. The prior net benefit calculations were restricted to first non-fatal events over 10 years. Baseline events were linearly projected from the estimate of baseline risk (**Appendix A Table 17**), such that, for example, out of 1,000 men with 10% 10-year coronary heart disease risk, 100 were predicted to have MIs (of which 32 cases could be prevented by using aspirin). In contrast, our approach derives a distribution of fatal and non-fatal preventable events, as predicted by the model, based on the risk factors representative of persons in each age, sex, and baseline CVD risk threshold. In this way, we predict far fewer MIs and strokes that may be prevented for each CVD risk group than the 2009 recommendation—even though more than one non-fatal event can be prevented for each person—as these events are subcomponents of the composite outcome for which CVD risk is selected upon (i.e., the combination of coronary death and fatal and non-fatal MI and stroke).[37] In addition, **Appendix A Table 17** reveals that the ratio of non-fatal to fatal events generally decreases with age, as first or subsequent events become more likely to be fatal. This distinction is important because the CVD prevention benefits to aspirin are found to be realized through the direct reduction in risk of non-fatal MI and ischemic stroke events—meaning, at a given level of baseline CVD risk, there may be relatively fewer of these events that can be prevented by aspirin among persons in older age groups.

The baseline population rate of GI bleeding used in the 2009 USPSTF aspirin recommendation came from an analysis of population-based databases in the United Kingdom and Spain;[56] in this study, we derived estimates from a population-based study conducted in Italy,[34] with age and sex adjustments made for the U.S. population. Although there are some differences—the largest of which are among men and women aged 50-59—estimated GI bleeding rates in the baseline population are generally similar in this study (**Appendix A Table 18**). What is notably different, however, is that our analysis incorporates estimates of age-adjusted case-fatality associated with GI bleeding events. Accounting for fatal GI bleeds can have a meaningful effect on net benefit calculations—particularly, for men and women aged 70-79 who might have otherwise expected positive lifetime net benefits without accounting for this harm (**Appendix A Table 13**, **Case 10**).

The approach to hemorrhagic stroke is also notably different. In the 2009 recommendation, the baseline rate of hemorrhagic stroke did not vary by age for men (for women, ischemic and hemorrhagic stroke were combined). In our analysis, hemorrhagic stroke incidence is determined by a risk equation derived from Framingham Heart Study data specifically for use in our model. Hemorrhagic stroke risk predictors include age, BMI, SBP, and smoking status. Therefore, hemorrhagic stroke rates in our analysis vary by age group and by baseline CVD risk. This also means that both benefits and harms scale with baseline CVD risk in our analysis, in contrast to benefits alone. The resulting baseline population rates of hemorrhagic stroke generated by our model compare well with those found in large U.S.-based cohort studies (**Appendix A Table 18**) and are generally much higher than assumed by the 2009 recommendation, in part offsetting the difference in the assumed increased relative risk of hemorrhagic stroke with aspirin use.

Another important distinction is that the microsimulation model used in our analysis accounts for the dynamics of competing risks among fatality by CVD, CRC, and GI bleeding and other causes of death in quantifying net benefits. The model also accounts for background use of secondary prevention following a CVD event. When the first non-fatal CVD event of a simulated person is

prevented or delayed by aspirin use, their use of aspirin, statins, and anti-hypertensive medications for secondary prevention also may be prevented or delayed. The prevention or delay of an initial non-fatal event also changes the risk of subsequent non-fatal and fatal events. This provides more realistic estimates of the marginal value of aspirin in primary prevention relative to secondary prevention. We also assume that aspirin therapy will be stopped immediately if adverse events are encountered.

Another difference and important strength in our approach is that the baseline 10-year CVD risk for each simulated individual is calculated using the ACC/AHA risk equation, which is separate from the model's risk engine. When assessing CVD risk, clinicians are likely to use the ACA/AHA or a similar 10-year risk calculator in daily practice. Because the risk calculator is separate from the model's risk engine, there is imperfect correlation between a simulated person's baseline line risk categorization and their CVD events as determined by the model. This parallels the imperfect correlation between baseline risk as predicted by a calculator in clinical decision-making and the realized patient experience with CVD over time, similar to that encountered in daily practice. **Appendix A Figures 2** and **3** illustrate this imperfect correlation and reflect patterns similar to those shown in other comparisons of the difference between observed outcomes and those predicted by the ACC/AHA risk calculator.[57-60] Despite the imperfect correlation, baseline event rates predicted by our model validate reasonably well to U.S. population event rates observed in NHANES data (**Appendix A Table 1**).

Another important strength to this study is in providing both short- and long-term outcomes. Standard guidance for the time horizon in health policy evaluations is to ensure a sufficient analytic window such that all important harms and benefits are captured.[52] Our results reveal that the lifetime horizon is needed to meet this standard and that the benefit-to-harm ratio generally increases over time—such that the largest average net benefit is realized with long-term aspirin use. There are several reasons for this. First, following the findings from the systematic evidence review, benefits to reducing CRC incidence are not realized until after 10 years of starting aspirin use. Second, the absolute risk of CVD and CRC generally increase at a greater rate with age than the risk of bleeding events. Third, and most important, the direct and indirect benefits from preventing non-fatal events can take time to accrue. For example, the direct benefits of preventing or delaying an ischemic stroke accumulate over time, due to the ongoing reduction in quality of life that a person would have otherwise endured after the serious event. However, even if an event has no discernible long-term effect on quality of life—such as is often the case with a non-fatal MI—the risk of future events or death is still increased. In this way, a prevented non-fatal CVD event often can confer lasting indirect benefits in averting or delaying future events or death that would have occurred counterfactually. These indirect downstream benefits are a major factor in explaining the large differences in net benefits often seen between the 20-year and lifetime horizons in our analysis. We recognize, however, that lifetime benefits and indirect outcomes may be extensively discounted or too abstract in the context of individual decision-making. For these reasons, we also provide 10- and 20-year outcomes for more comprehensive clinical context to informing shared decision-making.

The relationship between and valuation among benefits and harms from long-term aspirin use is complex. Another important contribution of this study is in providing life years and QALYs as outcome measures, in addition to specific fatal and non-fatal benefit and harm events. Life years

are an important measure because they incorporate differences in the expected length of life that may come from increased prevalence of fatal hemorrhage episodes, balanced against indirect reductions in CVD or CRC mortality. QALYs are an important measure because they incorporate both expected length of life and quality of life effects, balanced among all fatal and non-fatal benefit and harm events. Together, we believe these two measures are the best overall summary of—and are the most useful when assessing—the balance of benefits and harms from routine aspirin use. Still, we recognize that these composite measures may be abstract to interpret—or that patients may have personal preferences with respect to how to weigh the importance of specific benefit or harm events. For these reasons, the detailed outcomes presented in **Appendix A Tables 5-12** also provide important context for decision makers.

ModelHealth: CVD also incorporates race/ethnicity-specific CVD and CRC risk factors. The relationship between behaviors and CVD events over time is estimated using the strength of the Framingham Heart Study's considerable longitudinal data, but this comes with well-recognized limitations with respect to generalizability. By incorporating disparities in risk factors by race/ethnicity, the model provides estimates that are more generalizable to the U.S. population. However, it must be recognized that not all differences are necessarily accounted for, including any disparities in environmental risk exposure such as air pollution, utilization of other CVD preventive measures, and utilization of effective CVD treatments. Differences in predicted outcomes by race/ethnicity are not reported, but corresponding differences in CVD risk factors, CRC incidence, and CRC case-fatality rates may affect the relative net benefits that may be expected for specific persons or population groups.

Appendix A Table 19 compares the 10-year risk thresholds (of coronary heart disease for men and stroke for women) identified by the USPSTF in 2009 to the corresponding results from this study for which the benefits of using aspirin are predicted to exceed the harms in terms of net events over 10 years. Despite the numerous differences in the informing evidence and methodology—and the tools to estimate CVD risk thresholds themselves—positive net event thresholds (which exclude CRC in both cases) are of similar magnitude for men aged 40-59 and women aged 50-69. For men aged 60-69, we find positive net events are expected for men with 10-year CVD risk of 19% and higher (compared to 9% previously), and in contrast to prior findings, positive net event thresholds over 10 years were not identified in our analysis for men and women aged 70-79. Differences in findings for these age groups—and to a lesser extent, younger age groups—are primarily explained by the large differences in estimated baseline preventable CVD event rates for each risk threshold (**Appendix A Table 17**) and the approximately 40% difference in estimated rates of excess bleeding with aspirin use.

Comparison to Other Recent Analyses

A recent study by van Kruijsdijk et al[61] used long-term follow-up results from the Women's Health Study (WHS) to develop competing risk prediction models for the estimation of absolute risk reduction among CVD, cancer, and GI bleeding. Findings from WHS are included among our parameter estimates, and outcomes from this study concord with the average across other studies and others diverge from the broader evidence base. Specifically, over 10.1 years of average follow-up, WHS found no effect on non-fatal MI (RR = 1.01, 95% confidence interval

[CI]: 0.83, 1.24), concordant effects on non-fatal stroke (RR = 0.81, 95% CI: 0.67, 0.97), below average effects on serious MI bleeding (RR = 1.40, 95% CI: 1.07, 1.83), and above average effects on hemorrhagic stroke (RR = 1.24, 95% CI: 0.82, 1.87) [44]. Notably, a statistically significant effect on non-fatal MI was found among women aged 65 and older (RR = 0.66, 95% CI: 0.44-0.97). No statistically significant effect was found on total cancer (RR = 1.01, 95% CI: (0.94-1.08) or CRC (RR = 0.97, 95% CI: 0.77-1.24) during the trial period;[62] however, a highly concordant relative risk of 0.58 (95% CI: 0.41, 0.81) was found in this population during the 8 years post-trial.[45] Proportional hazard models estimated using trial-period data were used to predict changes in absolute risk for major CVD events, CRC, non-colorectal cancer, major GI bleeding, and death by another cause for 10- and 15-year periods. Overall, they found that harms generally exceed benefits for women younger than age 65, but that benefits modestly exceed harms for women aged 65 and older. **Appendix A Table 20** shows a comparison of the major CVD, CRC, and GI bleeding incidence findings with those in our study. Despite differences in underlying evidence and methods, our results over 10 and approximately 15 years are generally quite comparable. The only exception is the higher rate of prevented major CVD events in women aged 65 and older predicted by van Kruijsdijk et al., but this is readily explainable by the large reduction in non-fatal MI seen among this group in WHS.

Another recent study by Cuzick et al.[63] used a population-based incidence model to estimate the net difference in event rates over 15 years with prophylactic aspirin use in the general population of the United Kingdom (U.K.). In comparison to our model parameters, their literature review found relative risks for the incidence of non-fatal events to be 0.82 for MI, 0.95 for stroke, 0.65 for CRC, and 1.54 for major extracranial bleeding. They also found relative risks for mortality to be 0.95 for MI, 1.21 for stroke, 0.60 for CRC, and 1.60 for GI bleeding. Effects on both incidence and mortality were applied in their analysis. Another major difference was in finding relative risk reductions for incidence and mortality of esophageal, gastric, lung, prostrate, and breast cancers—although, three coauthors felt the evidence was still inconclusive with respect to lung, prostrate, and breast cancers. Net event rates were calculated using population incidence rates by age and sex in the U.K. over a 15 year period, with aspirin used actively for the first 10 years. CVD benefits were assumed only during the 10 years of active use, and cancer benefits are assumed for years 4-15. Overall, they found that net benefit events generally exceed net harms; however, cancers accounted for 61-80% of the net benefits they found and 30-36% of that was attributed to CRC reduction. **Appendix A Table 21** shows a comparison of the non-fatal MI, stroke, and GI bleeding incidence findings to those in our study. For that which can be compared, findings are generally consistent between studies, with differences in net events explainable by differential baseline event rates between the U.S. and U.K. populations and by the combined versus separated approach to aspirin's effect on stroke type.

Limitations

The results reflect average aspirin effectiveness as determined by the systematic reviews. As such, the results reflect cross-contamination of intervention and control groups that occurred in the abstracted clinical trials. Cross-contamination has two sources: participants assigned to the control group may choose to use aspirin, and participants assigned to the aspirin group may choose not to use aspirin (non-adherence). During an aspirin trial, there may be very few who

stop taking the placebo and start daily aspirin, but after the trial ends, those assigned to the placebo may begin daily aspirin use. This may impact effect sizes calculated in long-term follow-up studies. Adherence among persons volunteering for and selected into efficacy trials is likely to be higher than in the general population. It is not known by how much cross-contamination reduced the effect sizes used in the model. Although the effectiveness estimates used in the model do reflect some non-adherence, it is not known how the model's effect sizes compared to what would be observed with typical adherence levels and with a pure control group. We do expect, however, that the effectiveness of aspirin reflected in the model and these results should correspond with "good" adherence, insofar as they mirror a population willing to participate in an extended randomized controlled trial. Patients and providers may wish to consider the value and appropriateness of aspirin use for patients with lower expected adherence patterns differently.

Other possibly important limitations of the provided estimates include using the same effect size for all age groups. The systematic reviews did not find compelling evidence of differential effects by age group; therefore, we used the same relative aspirin impact for all age groups. It is not clear how robust homogenous relative risk effects are for all population groups—particularly, for those with low event rates or those not well-represented in the trial populations, such as those in their early 40s. Some aspirin trials included persons who enrolled or aged into their 80s, and we extended aspirin effects at the same levels for persons over the age of 80; however, we did not evaluate aspirin initiation for persons at these ages (nor for those younger than 40), due to their limited representation in the enrollment of the aspirin trials. Population data suggest that age-based inference may matter in some cases. For instance, excess GI bleeding risk from aspirin may be higher among persons younger than age 50.[34]

By design, both CVD and CRC mortality risk may be affected indirectly by aspirin use in our analysis. With respect to the relative risk of CVD mortality, the low-dose aspirin trials indicate that there may be a small reduction in risk, but this finding is not statistically significant (relative risk = 0.96, 95% confidence interval = 0.84 to 1.11).[13] Although we assumed no direct benefit in our base case analysis, risk of death from CVD may be reduced in our model as an indirect downstream effect proceeding the prevention of a non-fatal MI or ischemic stroke. **Appendix A Table 22** shows that although our analysis also finds small average reductions in CVD fatality with aspirin over 10 years through this indirect pathway (with relative risks ranging from 0.995 to 0.999), these results are still consistent with the non-statistically significant findings among the aspirin trials. With respect to CRC, evidence indicates that the relative risks of CRC incidence and mortality are both reduced with aspirin use. To avoid double-counting, we chose to directly model aspirin's effect on CRC incidence only. That is, when there are fewer cases of CRC, there also will be fewer cases of CRC mortality—all else held equal. **Appendix A Table 22** shows that the relative risk reductions in CRC mortality in our modeled populations—due to reduced CRC incidence alone and ranging from 0.73 to 0.86—are within the upper end of the confidence range observed among the trials (relative risk = 0.67, 95% confidence interval = 0.52 to 0.86).[14]

By simulating individuals, the model accounts for correlation between risk for CVD and CRC due to tobacco use. Hemorrhagic stroke risk also correlates with overall CVD risk. We did not, however, establish and incorporate into the model GI bleeding risk equations that would account

for correlation between GI bleed risk factors and CVD risk factors, such as tobacco use and diabetes, among others. The scope of the project did not allow for this advancement of methods. Careful determination of independent bleed risk factors in the general population and development of GI bleeding risk equations are important priorities for creating more precise estimates of net benefit from low-dose aspirin use.

These results naturally raise questions about whether there is an optimal age to stop aspirin use; however, evidence is lacking on the implications of aspirin discontinuation after long-term use. For example, it could be that the relative risk of harms diminishes with extended use of aspirin, and/or the relative risk of CVD could rebound to the same or a higher level when discontinuing aspirin after long-term use. It is also not clear how long after discontinuing sustained aspirin use the benefits to preventing CRC persist—or whether, as we potentially conservatively assumed in this study, the benefits cease immediately after stopping aspirin. Using a model to inform discontinuation decisions could be misleading without better data to support such analyses.

This analysis approached the decision to use aspirin from the perspective of a person's age, sex, and 10-year risk for CVD. Given the systematic evidence review findings of substantial benefit from aspirin for the prevention of CRC incidence, persons with elevated risk for CRC may have an interest in taking aspirin for this benefit alone. Stratifying net benefits by CRC risk was outside the scope of this analysis, but we believe results for persons at low 10-year CVD risk (for which the CRC share of benefits will be generally greatest) and the detailed outcomes presented in **Appendix A Tables 5-12** may be helpful for those approaching decisions to take aspirin from this perspective.

Accounting for the benefits and harms from aspirin with respect to stroke is challenging. It is widely believed that aspirin reduces the risk of ischemic stroke, but increases the risk for hemorrhagic stroke. The latter was not found to be statistically significant in the updated systematic review, but we included this harm in our decision analysis due to its biological plausibility and due to the lack of power in aspirin trials to detect statistically significant differences in this relatively rare event. Only two of the seven low-dose aspirin trials included in the updated systematic review reported non-fatal ischemic stroke independently;[13,38,40] therefore, the combined stroke relative risk observed across trials included hemorrhagic stroke events. We used this combined measure as the best estimate for the relative risk of ischemic stroke in our model. Although the rate of hemorrhagic stroke is much lower than for ischemic stroke, this approach should at least modestly—and systematically—underestimate the ischemic stroke reduction benefit conferred from routine aspirin use. This conservative approach may be appropriate, however, given the imprecision in measuring the increased risk of hemorrhagic stroke.

Finally, case-fatality rates for GI bleeding events are not well-established in the literature. Aspirin primary prevention trials do not show a difference in GI bleed mortality, but they do not have sufficient statistical power to show significant differences because deaths from GI bleeding are rare. At older ages, GI bleed and death risk are increased, and we have assumed a large jump in case-fatality rates from 3% to 19% between ages 60-79 and 80+. Better estimates of how age, sex, aspirin, and other possible risk factors interact to affect GI bleeding and case-fatality rates

may modify the net benefit findings—particularly, among older age groups (**Appendix A Tables 13-15, Cases 10 and 11**).

Conclusions and Future Research Needs

These results indicate that several population groups may benefit from taking aspirin for the primary prevention of CVD and CRC. Specifically, lifetime benefits are predicted to exceed harms among all men and women aged 40-69 with non-elevated bleeding risk. Net benefits are generally greater for persons at higher levels of 10-year CVD risk. For men and women aged 70-79, lifetime net outcomes are mixed: net life years are negative, but net QALYs are positive. Net benefits from aspirin over 10 and 20 years of use are generally much lower and may be negative. Net benefit calculations also favor early over delayed initiation of aspirin use for all men and women aged 40-69.

Discretion should be used when interpreting these results, as deterministic and probabilistic sensitivity analyses reveal meaningful uncertainty about the magnitude of net benefit. Net benefit calculations are most sensitive to uncertainty regarding the effect of low-dose aspirin on the increased risk of hemorrhagic stroke and in the primary prevention of CVD mortality. The relative risks of CRC incidence and ischemic stroke also introduce moderate uncertainty. Moreover, parameter estimates used in this study may not be reliable for populations underrepresented in the aspirin primary prevention trials (such as persons under age 50). A better understanding of the impact of aspirin by age group and the development of comprehensive risk equations for GI bleeding would improve confidence in and precision of the simulation results. Quality of life benefits from using aspirin may be considerably diminished among persons who dislike taking routine medications. Finally, future research may identify additional benefits (such as protective effects against other cancers) or harms that may substantially alter these findings. These sources of uncertainty and patient preferences should be carefully considered in shared decision-making.

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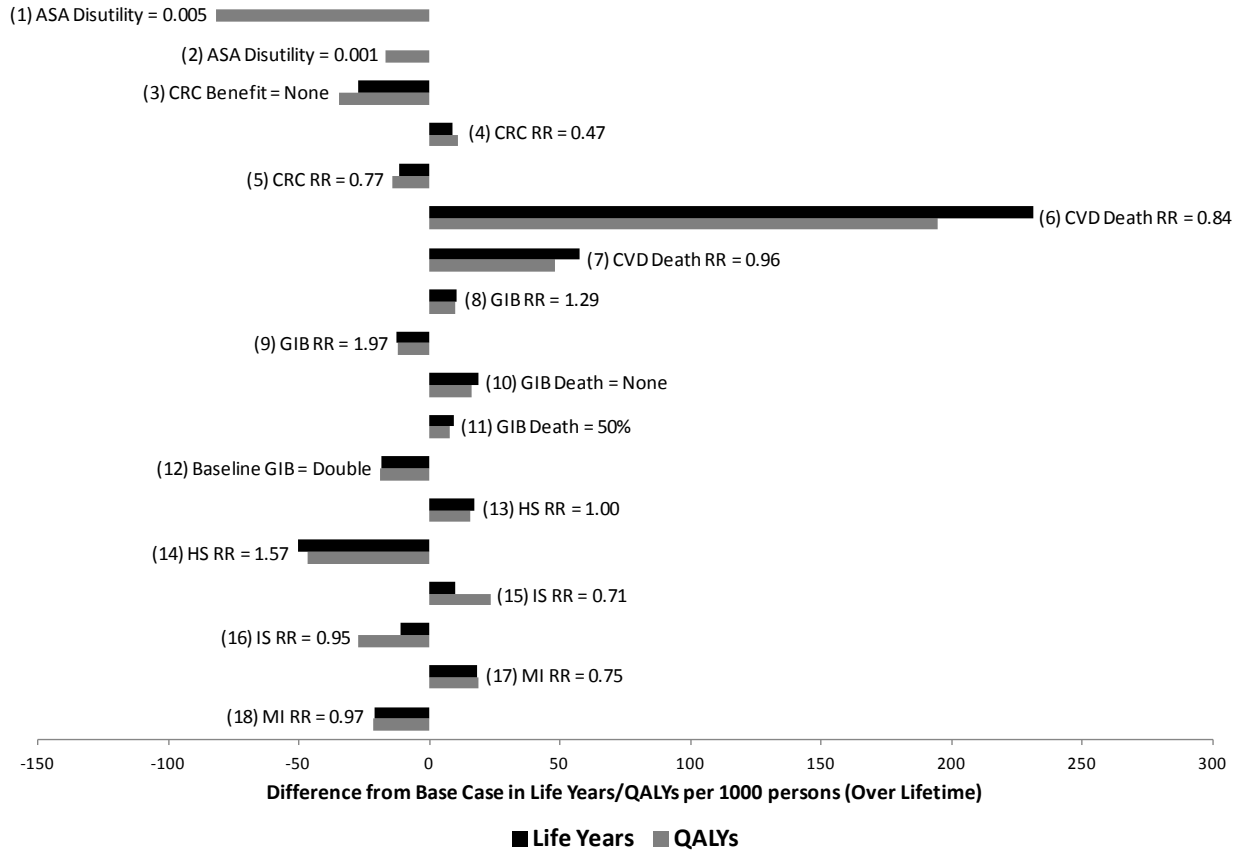
Figure 1. Comparisons in Lifetime Net Benefit From Taking Aspirin Averaged Across All Age, Sex, and Baseline CVD Risk Groups (KQs 1a-c, Deterministic Sensitivity)



Notes: ASA=acetylsalicylic acid (aspirin); CRC=colorectal cancer; RR=relative risk; CVD=cardiovascular disease; GIB=gastrointestinal bleeding; HS=hemorrhagic stroke; IS=ischemic stroke; MI=myocardial infarction; QALYs=quality-adjusted life years. Results reflect the difference (sensitivity) in lifetime net outcomes compared to the base case analysis, averaged across all age, sex, and baseline CVD groups. Each numbered item represents a one-way sensitivity analysis with the parameter changed as described. Case (4) CRC Benefit = None is equivalent to setting the CRC RR = 1. Case (10) GIB Death = None is equivalent to setting the case-fatality rates from GI bleeding to 0%. Case (12) Baseline GIB = Double is equivalent to doubling the baseline probabilities of GI bleeding. See Table 1 for additional detail.

Table 1. Key Model Parameters and Sensitivity Values

Parameter	Base case	Low effect	High effect	Other values	Source
Benefits					
All cancer, relative risk	1.00				Assumption [15]
CRC death, relative risk	1.00				Assumption [14]
CRC incidence (1-10 years), relative risk	1.00				Assumption [14]
CRC incidence (>10 years), relative risk†	0.60	0.77	0.47	1.00	[14, 45, 46]
CVD death, relative risk†	1.00	1.00	0.84	0.96	[13, 38-44]
Ischemic stroke (non-fatal), relative risk†	0.82	0.95	0.71		[13, 38, 40-44]
Myocardial infarction (non-fatal), relative risk†	0.85	0.97	0.75		[13, 38-44]
Harms					
GI bleeding (major), relative risk†	1.59	1.29	1.97		[13, 38-40, 43, 44]
Hemorrhagic stroke, relative risk†	1.14	1.00	1.57		[13, 38-40, 42-44]
Other parameters					
GI bleeding, baseline risk (per year)					
Men, 40-49	0.05%			0.10%	[34]
Men, 50-59	0.12%			0.24%	[34]
Men, 60-69	0.21%			0.42%	[34]
Men, 70-79	0.39%			0.78%	[34]
Men, 80+	0.61%			1.22%	[34]
Women, 40-49	0.03%			0.06%	[34]
Women, 50-59	0.07%			0.14%	[34]
Women, 60-69	0.13%			0.26%	[34]
Women, 70-79	0.23%			0.46%	[34]
Women, 80+	0.36%			0.72%	[34]
GI bleeding, case-fatality					
Age 40-59	1%	0%		0.5%	[35]
Age 60-79	3%	0%		1.5%	[35]
Age 80+	19%	0%		9.5%	[35]
Utility of taking aspirin daily	1.000	0.999	0.995		Assumption

Notes: CRC=colorectal cancer; CVD=cardiovascular disease; GI=gastrointestinal. Low- and high-effect sensitivity values are ordered by their differential magnitude from 1.00. Baseline GI bleeding risks are the probabilities of developing a GI bleed, with or without aspirin, by age and sex. GI bleeding case-fatalities represent the probability of dying from a GI bleed, by age. Aspirin use utilities are applied multiplicatively to the baseline health utility weight and are included in both Tables 1 and 2 for convenience and completeness. The symbol † indicates that the parameter is included in the probabilistic sensitivity analysis, with parameter values randomly drawn from a triangle distribution using the low, base case, and high values.

Table 2. Health Utility Weights

	First year/new event	Ongoing quality-of-life	Source
Baseline health utility weight			
No CVD conditions		0.872	[48, 50-53]
Relative health utility weight			
Colorectal cancer	0.700	0.700	Assumption
Congestive heart failure	0.786	0.786	[47, 49, 51-53]
GI bleeding	0.907	1.000	[47]
Hemorrhagic stroke	0.600	0.600	Assumption
Ischemic stroke	0.771	0.771	[47-52]
Myocardial Infarction	0.859	1.000	[47-49, 51, 53]
Taking aspirin, base case		1.000	Assumption
Taking aspirin, sensitivity #1		0.999	Assumption
Taking aspirin, sensitivity #2		0.995	Assumption

Notes: CVD=cardiovascular disease; GI=gastrointestinal. All health utility weights are applied multiplicatively to the baseline health utility weight. The quality-of-life reduction for colorectal cancer is applied for up to five years in the case of non-fatal episodes. First year/new event health utility weights are applied during the year of an incidence event or first year of disease onset; ongoing health utilities are applied in subsequent years. Aspirin use utilities are included in both Tables 1 and 2 for convenience and completeness.

Table 3. Estimated Distribution of ACC/AHA 10-Year ASCVD Risk by Sex and Age

ACC/AHA 10-year Risk %	Men				Women			
	40-49	**50-59**	**60-69**	**70-79**	**40-49**	**50-59**	**60-69**	**70-79**
	Population without prior CVD as share of total (percentage)							
0	1.7	0.0	0.0	0.0	21.5	0.9	0.0	0.0
1	16.8	0.4	0.0	0.0	41.8	20.2	0.2	0.0
2	19.2	3.2	0.0	0.0	15.0	21.4	3.3	0.0
3	15.5	7.0	0.1	0.0	6.4	14.3	7.0	0.0
4	11.1	8.8	0.3	0.0	3.7	9.7	8.3	0.0
5	7.6	9.7	1.2	0.0	2.2	6.1	8.2	0.3
6	5.5	9.3	2.2	0.0	1.3	4.6	8.0	0.5
7	4.0	7.4	3.0	0.0	0.7	3.2	7.1	1.1
8	2.9	6.6	3.6	0.1	0.7	2.4	5.9	1.5
9	2.1	5.4	4.8	0.2	0.3	1.6	4.8	1.6
10	1.6	4.5	4.8	0.3	0.3	1.3	4.7	1.9
11	1.1	3.9	4.8	0.6	0.2	0.9	4.2	2.4
12	0.9	3.3	4.5	0.7	0.1	0.6	3.6	2.1
13	0.6	2.7	4.2	0.8	0.1	0.5	2.7	3.0
14	0.7	2.4	4.0	1.1	0.1	0.5	2.4	3.0
15	0.4	1.9	3.8	1.4	0.0	0.3	2.0	2.9
16	0.4	1.5	3.7	1.5	0.1	0.3	2.0	2.9
17	0.4	1.2	3.1	1.4	0.1	0.2	1.4	3.0
18	0.2	1.1	3.0	1.6	0.1	0.2	1.4	2.8
19	0.2	0.9	2.7	1.9	0.0	0.1	1.2	2.9
20	0.2	0.8	2.3	2.2	0.0	0.1	0.9	3.0
0-20	93.0	82.2	55.9	13.8	94.7	89.6	79.1	34.8

Notes: ACC/AHA=American College of Cardiology/American Heart Association; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease. This table represents the distribution of 10-year CVD risk according to the AHA/ACC risk calculator in a 100,000-person U.S. population-representative random sample generated by the model for each age and sex group. The 0-20% totals do not sum to 100% for two reasons: 1) some CVD-free persons have a risk greater than 20%, and 2) the remaining population alive at these ages has a history of prior CVD. Risk levels are rounded to the nearest integer.

Table 4. Lifetime Net Benefit of Aspirin for Men and Women (KQ 1a)

% 10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Men				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	42.4 (33.7 to 51.1)	25.8 (18.4 to 33.1)	N/A	N/A
5	63.1 (54.1 to 72.0)	30.1 (22.4 to 37.8)	3.9 (-2.4 to 10.2)	N/A
10	79.7 (70.7 to 88.7)	46.5 (38.4 to 54.5)	10.9 (4.5 to 17.3)	-7.9 (-12.9 to -2.9)
15	90.8 (81.6 to 100.0)	52.7 (44.8 to 60.5)	19.0 (12.5 to 25.4)	-8.8 (-13.8 to -3.9)
20	87.2 (78.2 to 96.1)	69.2 (61.5 to 76.9)	20.7 (14.4 to 27.0)	-12.2 (-17.0 to -7.4)
	QALYs per 1000 persons (95% Confidence Interval)			
1	68.8 (60.7 to 76.9)	51.6 (44.8 to 58.4)	N/A	N/A
5	91.8 (83.6 to 100.0)	56.8 (49.7 to 63.8)	27.6 (21.9 to 33.3)	N/A
10	109.7 (101.4 to 117.9)	75.1 (67.8 to 82.4)	32.6 (26.7 to 38.6)	7.6 (3.1 to 12.2)
15	119.4 (110.9 to 127.8)	79.4 (72.2 to 86.6)	42.0 (36.0 to 48.0)	7.3 (2.8 to 11.8)
20	115.5 (107.1 to 123.9)	95.7 (88.5 to 102.9)	43.1 (37.3 to 48.8)	5.2 (0.8 to 9.6)
Women				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	28.3 (19.9 to 36.8)	11.5 (3.3 to 19.7)	1.4 (-5.5 to 8.3)	N/A
5	64.9 (54.5 to 75.2)	30.7 (21.8 to 39.6)	4.5 (-2.4 to 11.4)	-12.3 (-17.8 to -6.8)
10	77.5 (67.8 to 87.2)	41.7 (33.3 to 50.2)	13.3 (6.7 to 19.9)	-12.7 (-17.9 to -7.6)
15	78.9 (68.6 to 89.1)	58.6 (50.3 to 67.0)	20.2 (13.7 to 26.8)	-8.6 (-13.9 to -3.3)
20	90.1 (80.2 to 99.9)	62.2 (54.1 to 70.4)	20.3 (13.6 to 26.9)	-13.0 (-18.3 to -7.7)
	QALYs per 1000 persons (95% Confidence Interval)			
1	67.1 (59.2 to 75.1)	47.3 (39.8 to 54.7)	30.2 (23.9 to 36.4)	N/A
5	107.8 (98.2 to 117.4)	70.5 (62.3 to 78.8)	38.0 (31.6 to 44.5)	9.0 (3.9 to 14.0)
10	122.1 (113.1 to 131.2)	88.5 (80.4 to 96.5)	48.0 (41.7 to 54.4)	10.2 (5.4 to 15.0)
15	125.8 (116.2 to 135.3)	101.5 (93.5 to 109.4)	56.2 (50.0 to 62.5)	15.0 (10.0 to 20.0)
20	137.2 (127.9 to 146.5)	106.5 (98.7 to 114.3)	57.5 (51.3 to 63.8)	13.9 (9.0 to 18.7)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample.

Table 5. Net Benefit of Aspirin Over 20 Years for Men and Women (KQ 1b)

% 10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Men				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	0.0 (-1.2 to 1.2)	-2.7 (-4.5 to -0.8)	N/A	N/A
5	-0.1 (-1.8 to 1.5)	-2.2 (-4.3 to -0.1)	-6.3 (-8.9 to -3.7)	N/A
10	0.7 (-1.1 to 2.6)	1.8 (-0.9 to 4.5)	-4.0 (-6.9 to -1.2)	-10.9 (-14.5 to -7.4)
15	2.8 (0.8 to 4.8)	3.5 (0.7 to 6.2)	0.0 (-3.1 to 3.0)	-10.7 (-14.2 to -7.2)
20	4.0 (2.2 to 5.8)	11.6 (8.7 to 14.6)	-0.5 (-3.9 to 2.9)	-13.5 (-17.2 to -9.8)
	QALYs per 1000 persons (95% Confidence Interval)			
1	3.0 (1.6 to 4.3)	4.0 (2.1 to 5.9)	N/A	N/A
5	8.1 (6.4 to 9.8)	8.0 (5.8 to 10.2)	5.9 (3.4 to 8.4)	N/A
10	12.7 (10.7 to 14.7)	16.8 (14.1 to 19.5)	10.1 (7.2 to 12.9)	1.9 (-1.4 to 5.2)
15	14.9 (12.8 to 17.1)	19.7 (17.0 to 22.5)	16.8 (13.8 to 19.8)	2.8 (-0.5 to 6.1)
20	17.9 (15.8 to 19.9)	30.0 (27.0 to 32.9)	17.2 (13.9 to 20.4)	1.4 (-2.1 to 4.9)
Women				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	-0.4 (-1.3 to 0.5)	-2.2 (-3.6 to -0.8)	-3.8 (-5.8 to -1.8)	N/A
5	-0.3 (-1.7 to 1.2)	-3.1 (-5.4 to -0.8)	-4.4 (-6.9 to -2.0)	-11.9 (-14.9 to -8.9)
10	1.1 (-0.4 to 2.6)	0.0 (-2.5 to 2.4)	-3.7 (-6.7 to -0.7)	-13.1 (-16.6 to -9.7)
15	2.3 (0.7 to 3.9)	3.0 (0.6 to 5.5)	-1.1 (-4.1 to 2.0)	-12.7 (-16.3 to -9.2)
20	1.0 (-0.7 to 2.8)	2.3 (-0.3 to 4.9)	-0.4 (-3.6 to 2.8)	-14.4 (-18.4 to -10.5)
	QALYs per 1000 persons (95% Confidence Interval)			
1	4.0 (2.8 to 5.2)	4.3 (2.7 to 5.9)	5.2 (3.1 to 7.2)	N/A
5	9.2 (7.5 to 10.9)	11.2 (8.8 to 13.6)	10.9 (8.3 to 13.5)	0.9 (-2.0 to 3.8)
10	13.1 (11.4 to 14.8)	19.8 (17.2 to 22.5)	16.7 (13.6 to 19.9)	3.3 (0.0 to 6.5)
15	15.6 (13.7 to 17.4)	24.9 (22.2 to 27.6)	23.1 (20.0 to 26.2)	5.6 (2.1 to 9.0)
20	14.9 (13.0 to 16.8)	25.3 (22.4 to 28.1)	25.1 (21.8 to 28.4)	7.4 (3.7 to 11.1)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample.

Table 6. Net Benefit of Aspirin Over 10 Years for Men and Women (KQ 1c)

% 10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Men				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	-0.3 (-0.6 to -0.1)	-0.8 (-1.2 to -0.3)	N/A	N/A
5	-0.3 (-0.7 to 0.0)	-1.3 (-1.8 to -0.8)	-2.4 (-3.2 to -1.6)	N/A
10	-0.7 (-1.1 to -0.2)	-1.3 (-1.9 to -0.8)	-2.6 (-3.4 to -1.8)	-4.7 (-5.8 to -3.6)
15	-0.8 (-1.3 to -0.3)	-1.5 (-2.2 to -0.8)	-2.7 (-3.7 to -1.8)	-4.0 (-5.0 to -2.9)
20	-0.1 (-0.4 to 0.1)	-0.1 (-0.8 to 0.6)	-3.0 (-4.1 to -1.9)	-6.5 (-7.8 to -5.1)
	QALYs per 1000 persons (95% Confidence Interval)			
1	-0.3 (-0.6 to 0.0)	-0.5 (-1.0 to -0.1)	N/A	N/A
5	0.7 (0.3 to 1.2)	-0.3 (-0.9 to 0.2)	-1.6 (-2.4 to -0.8)	N/A
10	1.4 (0.8 to 2.0)	1.3 (0.6 to 1.9)	-0.5 (-1.4 to 0.3)	-2.5 (-3.6 to -1.5)
15	1.6 (1.0 to 2.1)	1.7 (0.9 to 2.5)	0.4 (-0.5 to 1.3)	-1.8 (-2.8 to -0.7)
20	2.9 (2.5 to 3.4)	4.7 (3.8 to 5.5)	1.1 (0.0 to 2.3)	-2.9 (-4.2 to -1.5)
Women				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	-0.2 (-0.4 to 0.0)	-0.6 (-0.9 to -0.3)	-2.0 (-2.7 to -1.3)	N/A
5	-0.5 (-0.9 to -0.2)	-1.6 (-2.2 to -0.9)	-2.0 (-2.7 to -1.3)	-2.8 (-3.6 to -2.0)
10	-0.3 (-0.7 to 0.0)	-1.3 (-1.9 to -0.7)	-2.1 (-2.9 to -1.3)	-3.5 (-4.5 to -2.6)
15	0.0 (-0.3 to 0.3)	-1.0 (-1.7 to -0.3)	-2.3 (-3.2 to -1.4)	-4.4 (-5.4 to -3.3)
20	-0.6 (-1.0 to -0.1)	-1.3 (-2.0 to -0.7)	-3.1 (-4.1 to -2.1)	-5.6 (-6.9 to -4.4)
	QALYs per 1000 persons (95% Confidence Interval)			
1	0.1 (-0.2 to 0.3)	-0.3 (-0.7 to 0.1)	-1.6 (-2.3 to -0.9)	N/A
5	0.8 (0.3 to 1.3)	0.4 (-0.3 to 1.1)	0.2 (-0.5 to 0.9)	-1.9 (-2.7 to -1.1)
10	1.8 (1.3 to 2.2)	2.4 (1.7 to 3.2)	2.0 (1.0 to 2.9)	-0.7 (-1.7 to 0.2)
15	2.6 (2.1 to 3.1)	3.8 (2.9 to 4.6)	3.8 (2.7 to 4.8)	-0.5 (-1.6 to 0.6)
20	2.1 (1.5 to 2.6)	3.7 (2.8 to 4.5)	4.0 (2.8 to 5.2)	0.2 (-1.1 to 1.5)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample.

Table 7. Marginal Lifetime Net Benefit From Taking Aspirin Now Versus Delaying 10 Years (KQ 2)

10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69
Men			
	Net Life Years per 1000 persons (95% Confidence Interval)		
1	12.5 (7.7 to 17.2)	11.6 (7.5 to 15.7)	N/A
5	23.9 (19.1 to 28.7)	17.1 (12.1 to 22.2)	8.0 (3.5 to 12.4)
10	28.1 (22.2 to 34.1)	27.1 (21.4 to 32.9)	14.0 (9.2 to 18.7)
15	36.7 (30.5 to 42.8)	29.7 (24.1 to 35.4)	18.9 (14.0 to 23.8)
20	39.7 (33.8 to 45.7)	40.3 (34.2 to 46.5)	19.2 (13.8 to 24.5)
	QALYs per 1000 persons (95% Confidence Interval)		
1	14.7 (10.3 to 19.1)	16.3 (12.5 to 20.2)	N/A
5	29.1 (24.6 to 33.5)	24.3 (19.7 to 29.0)	17.2 (13.2 to 21.3)
10	35.6 (30.1 to 41.1)	37.3 (32.0 to 42.6)	24.0 (19.6 to 28.4)
15	43.9 (38.2 to 49.6)	39.7 (34.6 to 44.9)	30.1 (25.5 to 34.6)
20	47.3 (41.7 to 52.9)	52.0 (46.3 to 57.7)	31.4 (26.5 to 36.3)
Women			
	Net Life Years per 1000 persons (95% Confidence Interval)		
1	9.4 (5.3 to 13.6)	8.3 (3.9 to 12.7)	10.5 (6.1 to 14.9)
5	24.3 (18.4 to 30.2)	16.5 (10.6 to 22.5)	14.0 (9.2 to 18.8)
10	29.1 (23.4 to 34.9)	25.7 (20.1 to 31.4)	15.4 (10.4 to 20.4)
15	32.7 (26.4 to 39.0)	32.0 (25.8 to 38.3)	21.5 (16.2 to 26.8)
20	28.2 (22.8 to 33.6)	34.0 (27.9 to 40.2)	20.8 (15.4 to 26.1)
	QALYs per 1000 persons (95% Confidence Interval)		
1	12.9 (9.0 to 16.8)	13.6 (9.5 to 17.6)	16.7 (12.7 to 20.7)
5	31.3 (25.8 to 36.8)	27.5 (22.0 to 33.0)	25.0 (20.5 to 29.5)
10	39.1 (33.6 to 44.5)	41.5 (36.1 to 46.9)	30.5 (25.6 to 35.4)
15	42.8 (37.0 to 48.6)	48.2 (42.3 to 54.1)	39.3 (34.3 to 44.4)
20	39.5 (34.5 to 44.6)	49.1 (43.3 to 54.9)	39.5 (34.5 to 44.5)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference in net benefit from starting aspirin at model baseline/initiation versus waiting 10 years. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample.

Table 8. Probabilistic Sensitivity in Net Benefit From Taking Aspirin for Men and Women at 10% CVD Risk (KQs 1a-c)

	Lifetime Outcomes			20-yr Outcomes			10-yr Outcomes		
Age	**Mean**	**Lower 95%**	**Upper 95%**	**Mean**	**Lower 95%**	**Upper 95%**	**Mean**	**Lower 95%**	**Upper 95%**
Men									
				Net Life Years per 1000 persons (95% Confidence Interval)					
40-49	165.8	23.8	307.8	24.1	-6.5	54.8	5.1	-1.7	11.9
50-59	150.9	11.5	290.3	40.3	-11.6	92.2	8.5	-3.9	20.9
60-69	86.1	-19.2	191.4	39.5	-16.3	95.3	9.5	-4.9	23.8
70-79	44.4	-28.2	116.9	29.9	-25.9	85.7	8.1	-8.3	24.5
				QALYs per 1000 persons (95% Confidence Interval)					
40-49	178.2	50.4	306.1	30.8	2.6	59.0	5.8	-0.3	12.0
50-59	160.3	35.8	284.7	47.8	0.5	95.0	9.0	-2.1	20.1
60-69	93.8	-0.2	187.8	45.7	-4.7	96.1	9.1	-3.6	21.9
70-79	50.6	-13.8	115.0	35.3	-14.5	85.0	7.5	-6.9	21.9
Women									
				Net Life Years per 1000 persons (95% Confidence Interval)					
40-49	167.1	19.7	314.6	20.7	-1.9	43.3	4.4	0.0	8.8
50-59	134.5	0.6	268.3	31.6	-9.7	72.9	6.8	-2.5	16.0
60-69	83.3	-21.8	188.3	31.1	-17.1	79.4	6.6	-5.2	18.4
70-79	42.2	-32.7	117.1	27.7	-22.9	78.4	8.9	-4.4	22.1
				QALYs per 1000 persons (95% Confidence Interval)					
40-49	192.0	57.4	326.5	27.8	6.2	49.4	5.2	1.1	9.3
50-59	161.9	40.4	283.4	45.7	6.7	84.7	8.9	0.2	17.5
60-69	104.3	9.6	198.9	44.4	-0.1	88.8	8.7	-2.3	19.6
70-79	54.2	-12.9	121.4	36.1	-9.7	81.9	9.1	-2.8	21.1

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; yr=year. Results represent the mean value and 95% confidence interval calculated from a probabilistic Monte Carlo sensitivity analysis with 500 replications of population samples of 100,000. All results in the table are based on populations with a 10-year 10% CVD risk level are based on the ACC/AHA risk calculator rounded to the nearest integer at model baseline/initiation.

Appendix A Table 1. Comparison of Baseline Modeled CVD Event Rates With National Prevalence Estimates

	Myocardial infarction		Ischemic stroke	
	NHANES (2001-2010)	ModelHealth: CVD	NHANES (2001-2010)	ModelHealth: CVD
	Percent of population with history of prior event			
Men and women				
Age 40-49	1.5%	2.3%	1.6%	1.7%
Age 50-59	4.0%	4.7%	2.3%	2.6%
Age 60-69	8.4%	8.5%	5.9%	4.8%
Age 70-79	12.0%	13.2%	9.3%	10.0%
Men only				
Age 40-49	1.7%	3.0%	0.8%	1.0%
Age 50-59	5.4%	6.4%	2.2%	2.0%
Age 60-69	13.1%	11.6%	6.1%	4.1%
Age 70-79	18.7%	18.7%	8.9%	9.7%
Women only				
Age 40-49	1.3%	1.6%	2.4%	2.4%
Age 50-59	2.7%	3.1%	2.5%	3.2%
Age 60-69	4.6%	5.9%	5.8%	5.4%
Age 70-79	7.4%	9.3%	9.6%	10.2%

Notes: NHANES=National Health and Nutrition Examination Survey; CVD=cardiovascular disease. This table compares CVD prevalence at various ages between NHANES 2001-2010 combined data and results from the ModelHealth: CVD model. The model run represented here is based on a birth cohort, starting at age 40, with hypertension screening and treatment, cholesterol screening and treatment, and aspirin for primary and secondary prevention all implemented and adopted at contemporary rates. For comparison purposes of the cross-sectional and longitudinal datasets, outcomes are calculated for the age range from NHANES and the mid-point of the age range from the ModelHealth: CVD output; this methodological difference can explain some small discrepancies.

Appendix A Table 2. Lifetime Discounted Net Benefit of Aspirin for Men and Women (KQ 1a)

% 10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Men				
	Discounted Net Life Years per 1000 persons (95% Confidence Interval)			
1	13.1 (9.9 to 16.3)	8.6 (5.3 to 11.8)	N/A	N/A
5	21.6 (18.1 to 25.1)	10.7 (7.2 to 14.2)	-0.6 (-3.8 to 2.7)	N/A
10	28.4 (24.7 to 32.0)	19.1 (15.2 to 23.0)	3.3 (-0.1 to 6.7)	-6.8 (-9.9 to -3.7)
15	33.1 (29.3 to 36.9)	22.3 (18.4 to 26.1)	7.9 (4.4 to 11.4)	-7.0 (-10.1 to -4.0)
20	33.6 (29.9 to 37.4)	31.7 (27.9 to 35.6)	8.7 (5.1 to 12.3)	-9.6 (-12.7 to -6.5)
	Discounted QALYs per 1000 persons (95% Confidence Interval)			
1	23.9 (20.9 to 27.0)	21.1 (18.0 to 24.2)	N/A	N/A
5	35.8 (32.5 to 39.1)	24.9 (21.6 to 28.1)	12.9 (9.9 to 15.9)	N/A
10	44.6 (41.1 to 48.1)	35.7 (32.1 to 39.3)	16.5 (13.3 to 19.8)	3.4 (0.5 to 6.2)
15	49.0 (45.4 to 52.7)	38.5 (34.9 to 42.1)	22.5 (19.2 to 25.8)	3.5 (0.7 to 6.3)
20	49.9 (46.2 to 53.5)	48.6 (44.9 to 52.3)	23.4 (20.0 to 26.7)	2.1 (-0.8 to 5.0)
Women				
	Discounted Net Life Years per 1000 persons (95% Confidence Interval)			
1	8.3 (5.4 to 11.3)	2.8 (-0.5 to 6.1)	-1.2 (-4.5 to 2.1)	N/A
5	20.5 (16.7 to 24.3)	10.3 (6.3 to 14.3)	0.3 (-3.2 to 3.8)	-8.6 (-11.8 to -5.4)
10	26.2 (22.5 to 29.9)	16.0 (12.1 to 19.9)	4.5 (1.0 to 8.1)	-9.2 (-12.3 to -6.0)
15	27.2 (23.3 to 31.1)	24.0 (20.1 to 27.9)	8.3 (4.7 to 11.8)	-7.3 (-10.5 to -4.0)
20	30.1 (26.4 to 33.9)	25.2 (21.3 to 29.1)	8.4 (4.7 to 12.0)	-9.9 (-13.3 to -6.6)
	Discounted QALYs per 1000 persons (95% Confidence Interval)			
1	23.6 (20.7 to 26.6)	18.8 (15.7 to 22.0)	13.5 (10.4 to 16.5)	N/A
5	40.1 (36.4 to 43.8)	31.1 (27.3 to 35.0)	19.0 (15.7 to 22.4)	4.0 (1.0 to 7.0)
10	47.8 (44.2 to 51.4)	41.5 (37.6 to 45.3)	25.4 (21.9 to 28.9)	5.3 (2.3 to 8.2)
15	50.0 (46.2 to 53.8)	48.7 (44.9 to 52.6)	31.0 (27.5 to 34.5)	8.0 (4.9 to 11.2)
20	53.5 (49.9 to 57.2)	50.8 (47.0 to 54.7)	32.1 (28.6 to 35.7)	8.0 (4.9 to 11.1)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample. Results in this table are discounted to present value using a 3% discount rate.

Appendix A Table 3. Discounted Net Benefit of Aspirin Over 20 Years for Men and Women (KQ 1b)

% 10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Men				
	Discounted Net Life Years per 1000 persons (95% Confidence Interval)			
1	-0.1 (-0.9 to 0.7)	-1.9 (-3.2 to -0.7)	N/A	N/A
5	-0.2 (-1.3 to 0.8)	-1.8 (-3.2 to -0.4)	-4.7 (-6.5 to -2.9)	N/A
10	0.2 (-1.0 to 1.5)	0.7 (-1.1 to 2.5)	-3.3 (-5.2 to -1.3)	-8.3 (-10.7 to -5.9)
15	1.5 (0.1 to 2.8)	1.7 (-0.2 to 3.6)	-0.8 (-2.9 to 1.2)	-7.9 (-10.3 to -5.6)
20	2.3 (1.2 to 3.5)	7.2 (5.2 to 9.2)	-1.2 (-3.5 to 1.2)	-10.3 (-12.9 to -7.7)
	Discounted QALYs per 1000 persons (95% Confidence Interval)			
1	1.7 (0.9 to 2.6)	2.3 (1.0 to 3.6)	N/A	N/A
5	5.2 (4.1 to 6.4)	4.9 (3.4 to 6.3)	3.3 (1.5 to 5.0)	N/A
10	8.3 (6.9 to 9.7)	10.9 (9.0 to 12.7)	6.2 (4.3 to 8.1)	0.5 (-1.7 to 2.8)
15	9.8 (8.3 to 11.2)	12.8 (10.9 to 14.7)	10.7 (8.6 to 12.8)	1.2 (-1.0 to 3.5)
20	11.9 (10.6 to 13.3)	20.1 (18.0 to 22.1)	11.1 (8.9 to 13.4)	0.2 (-2.3 to 2.6)
Women				
	Discounted Net Life Years per 1000 persons (95% Confidence Interval)			
1	-0.3 (-0.9 to 0.3)	-1.6 (-2.5 to -0.6)	-2.9 (-4.3 to -1.5)	N/A
5	-0.4 (-1.3 to 0.6)	-2.4 (-4.0 to -0.9)	-3.3 (-5.0 to -1.7)	-8.3 (-10.4 to -6.3)
10	0.6 (-0.4 to 1.5)	-0.5 (-2.1 to 1.2)	-2.9 (-5.0 to -0.9)	-9.3 (-11.6 to -7.0)
15	1.4 (0.4 to 2.4)	1.5 (-0.1 to 3.2)	-1.4 (-3.4 to 0.7)	-9.3 (-11.7 to -6.9)
20	0.4 (-0.7 to 1.6)	1.0 (-0.8 to 2.7)	-1.1 (-3.3 to 1.1)	-10.7 (-13.4 to -7.9)
	Discounted QALYs per 1000 persons (95% Confidence Interval)			
1	2.5 (1.7 to 3.3)	2.6 (1.5 to 3.7)	2.8 (1.4 to 4.2)	N/A
5	5.9 (4.8 to 7.1)	7.1 (5.4 to 8.8)	6.9 (5.1 to 8.6)	0.0 (-1.9 to 2.0)
10	8.7 (7.5 to 9.8)	13.0 (11.2 to 14.8)	11.0 (8.9 to 13.2)	1.8 (-0.4 to 4.0)
15	10.4 (9.2 to 11.7)	16.6 (14.7 to 18.4)	15.5 (13.4 to 17.7)	3.3 (0.9 to 5.7)
20	9.9 (8.6 to 11.2)	16.8 (14.8 to 18.7)	16.9 (14.5 to 19.2)	4.7 (2.1 to 7.3)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample. Results in this table are discounted to present value using a 3% discount rate.

Appendix A Table 4. Discounted Net Benefit of Aspirin Over 10 Years for Men and Women (KQ 1c)

% 10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Men				
	Discounted Net Life Years per 1000 persons (95% Confidence Interval)			
1	-0.3 (-0.4 to -0.1)	-0.6 (-1.0 to -0.3)	N/A	N/A
5	-0.3 (-0.6 to 0.0)	-1.1 (-1.5 to -0.7)	-2.0 (-2.7 to -1.4)	N/A
10	-0.5 (-0.9 to -0.1)	-1.1 (-1.5 to -0.6)	-2.1 (-2.8 to -1.5)	-3.9 (-4.8 to -3.0)
15	-0.7 (-1.1 to -0.2)	-1.3 (-1.8 to -0.7)	-2.3 (-3.1 to -1.5)	-3.3 (-4.2 to -2.4)
20	-0.1 (-0.3 to 0.1)	-0.1 (-0.7 to 0.5)	-2.5 (-3.5 to -1.6)	-5.4 (-6.5 to -4.2)
	Discounted QALYs per 1000 persons (95% Confidence Interval)			
1	-0.3 (-0.5 to 0.0)	-0.5 (-0.9 to -0.1)	N/A	N/A
5	0.6 (0.2 to 1.0)	-0.3 (-0.7 to 0.2)	-1.3 (-2.0 to -0.7)	N/A
10	1.2 (0.7 to 1.7)	1.1 (0.5 to 1.6)	-0.5 (-1.2 to 0.2)	-2.2 (-3.1 to -1.3)
15	1.3 (0.9 to 1.8)	1.4 (0.7 to 2.1)	0.3 (-0.5 to 1.1)	-1.5 (-2.4 to -0.7)
20	2.5 (2.1 to 2.9)	3.9 (3.2 to 4.6)	0.9 (0.0 to 1.9)	-2.4 (-3.5 to -1.3)
Women				
	Discounted Net Life Years per 1000 persons (95% Confidence Interval)			
1	-0.1 (-0.3 to 0.0)	-0.5 (-0.7 to -0.3)	-1.7 (-2.2 to -1.1)	N/A
5	-0.4 (-0.7 to -0.2)	-1.3 (-1.8 to -0.8)	-1.7 (-2.2 to -1.1)	-2.3 (-3.0 to -1.7)
10	-0.3 (-0.5 to 0.0)	-1.1 (-1.6 to -0.6)	-1.7 (-2.4 to -1.1)	-2.9 (-3.7 to -2.1)
15	0.0 (-0.2 to 0.2)	-0.8 (-1.4 to -0.3)	-1.9 (-2.7 to -1.2)	-3.6 (-4.5 to -2.7)
20	-0.5 (-0.9 to -0.1)	-1.1 (-1.6 to -0.6)	-2.6 (-3.4 to -1.8)	-4.7 (-5.7 to -3.6)
	Discounted QALYs per 1000 persons (95% Confidence Interval)			
1	0.0 (-0.2 to 0.3)	-0.3 (-0.6 to 0.1)	-1.4 (-2.0 to -0.8)	N/A
5	0.7 (0.3 to 1.0)	0.4 (-0.2 to 1.0)	0.2 (-0.5 to 0.8)	-1.6 (-2.3 to -1.0)
10	1.5 (1.1 to 1.9)	2.0 (1.4 to 2.7)	1.6 (0.8 to 2.4)	-0.6 (-1.4 to 0.2)
15	2.2 (1.8 to 2.6)	3.2 (2.5 to 3.8)	3.2 (2.3 to 4.0)	-0.4 (-1.3 to 0.5)
20	1.8 (1.3 to 2.2)	3.1 (2.3 to 3.8)	3.3 (2.3 to 4.3)	0.2 (-0.9 to 1.3)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample. Results in this table are discounted to present value using a 3% discount rate.

Appendix A Table 5. Detailed Benefits and Harms From Aspirin Use for Men Aged 40-49 (KQs 1a-c)

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	18.8	8.0	31.6	3.2	14.9	3.4	32.5	1.5	1.9	1.3	42.4	68.8	15.7
5	21.0	9.8	36.2	3.7	14.9	3.7	29.0	1.2	1.5	1.2	63.1	91.8	24.6
10	24.6	10.2	41.4	4.1	15.4	3.7	25.4	1.0	1.4	1.0	79.7	109.7	34.5
15	27.6	10.6	45.6	5.0	13.9	3.3	24.2	1.1	1.4	1.0	90.8	119.4	39.2
20	28.1	10.3	45.5	4.7	13.2	3.1	23.1	1.1	1.2	1.0	87.2	115.5	39.2
20-year outcomes													
1	6.8	1.4	8.5	0.1	2.5	0.5	10.4	0.5	0.1	0.3	0.0	3.0	0.2
5	10.7	3.3	14.8	0.3	3.7	0.7	12.6	0.4	0.3	0.4	-0.1	8.1	5.8
10	14.8	4.4	20.4	0.7	4.7	0.8	11.5	0.5	0.2	0.5	0.7	12.7	13.8
15	17.8	4.7	24.1	1.0	4.1	0.8	11.1	0.5	0.2	0.5	2.8	14.9	17.6
20	18.8	5.4	26.2	1.3	4.3	0.8	10.8	0.5	0.2	0.4	4.0	17.9	20.5
10-year outcomes													
1	2.3	0.3	2.7	0.0	0.0	0.0	3.6	0.2	0.1	0.1	-0.3	-0.3	-1.1
5	4.5	1.2	5.8	0.0	0.0	0.0	5.0	0.2	0.1	0.1	-0.3	0.7	0.6
10	7.3	1.6	9.1	0.1	0.0	0.0	5.1	0.3	0.1	0.2	-0.7	1.4	3.8
15	8.8	1.9	11.1	0.1	0.0	0.0	4.7	0.3	0.1	0.1	-0.8	1.6	6.2
20	9.9	2.3	12.5	0.1	0.0	0.0	4.9	0.3	0.0	0.2	-0.1	2.9	7.4

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Appendix A Table 6. Detailed Benefits and Harms From Aspirin Use for Women Aged 40-49 (KQs 1a-c)

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	9.8	13.2	27.0	2.5	14.1	3.5	26.4	1.7	1.9	1.4	28.3	67.1	15.5
5	12.4	15.1	33.1	3.7	15.4	4.3	21.4	2.1	1.6	1.9	64.9	107.8	28.7
10	14.0	15.6	36.3	3.9	16.2	4.1	21.2	1.5	1.4	1.4	77.5	122.1	33.7
15	15.2	17.0	38.9	4.5	14.8	3.4	19.4	1.4	1.2	1.4	78.9	125.8	37.4
20	15.9	17.2	40.3	4.3	15.4	4.0	19.0	1.1	1.5	1.1	90.1	137.2	39.9
20-year outcomes													
1	3.4	2.3	5.9	0.1	2.6	0.4	7.9	0.5	0.1	0.3	-0.4	4.0	0.2
5	5.7	4.5	10.8	0.3	3.4	0.8	7.1	0.7	0.1	0.4	-0.3	9.2	6.7
10	7.3	5.4	13.7	0.3	3.9	0.7	7.6	0.6	0.1	0.4	1.1	13.1	9.7
15	8.2	6.3	15.5	0.6	3.6	0.6	7.1	0.6	0.1	0.5	2.3	15.6	12.0
20	8.7	6.1	15.9	0.4	4.0	0.6	6.8	0.6	0.2	0.4	1.0	14.9	12.9
10-year outcomes													
1	1.1	0.6	1.7	0.0	0.0	0.0	2.9	0.1	0.0	0.0	-0.2	0.1	-1.3
5	2.5	1.7	4.3	0.0	0.0	0.0	2.7	0.3	0.0	0.1	-0.5	0.8	1.3
10	3.6	2.2	6.0	0.0	0.0	0.0	3.0	0.2	0.0	0.1	-0.3	1.8	2.8
15	3.8	2.5	6.5	0.1	0.0	0.0	2.6	0.2	0.0	0.0	0.0	2.6	3.8
20	4.4	2.5	7.1	0.1	0.0	0.0	2.6	0.3	0.0	0.1	-0.6	2.1	4.3

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Appendix A Table 7. Detailed Benefits and Harms From Aspirin Use for Men Aged 50-59 (KQs 1a-c)

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	15.1	7.8	26.9	2.8	14.0	3.3	34.7	1.4	2.2	1.1	25.8	51.6	7.6
5	17.1	8.6	30.3	3.3	14.0	3.4	30.7	1.5	2.0	1.4	30.1	56.8	15.4
10	20.1	10.5	36.1	3.6	13.9	3.0	28.9	1.1	1.8	0.9	46.5	75.1	23.6
15	23.9	10.6	41.6	4.8	12.1	2.3	26.4	1.4	1.5	1.3	52.7	79.4	30.7
20	25.0	11.7	43.9	5.0	12.2	2.7	25.2	1.1	1.3	1.0	69.2	95.7	34.8
20-year outcomes													
1	7.3	2.9	10.6	0.2	4.3	0.7	16.9	0.7	0.5	0.5	-2.7	4.0	-2.5
5	10.5	4.1	15.4	0.6	5.6	1.1	17.6	0.9	0.5	0.7	-2.2	8.0	3.1
10	14.7	5.9	22.4	1.3	6.8	1.2	18.5	0.7	0.6	0.6	1.8	16.8	11.3
15	18.3	7.0	28.3	2.0	6.3	0.9	17.4	0.9	0.5	0.8	3.5	19.7	18.3
20	20.3	7.9	32.1	2.7	6.9	1.3	17.3	0.8	0.4	0.7	11.6	30.0	23.6
10-year outcomes													
1	2.5	0.9	3.4	0.0	0.0	0.0	7.3	0.2	0.1	0.1	-0.8	-0.5	-4.1
5	4.7	1.3	6.0	0.0	0.0	0.0	8.0	0.4	0.2	0.2	-1.3	-0.3	-2.4
10	7.1	2.4	9.8	0.2	0.0	0.0	8.6	0.4	0.2	0.3	-1.3	1.3	1.0
15	9.4	3.0	13.0	0.2	0.0	0.0	8.5	0.5	0.2	0.4	-1.5	1.7	4.2
20	11.7	4.0	16.5	0.6	0.0	0.0	8.7	0.4	0.1	0.2	-0.1	4.7	8.0

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Appendix A Table 8. Detailed Benefits and Harms From Aspirin Use for Women Aged 50-59 (KQs 1a-c)

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	8.2	12.1	23.3	2.1	13.7	3.4	26.3	1.9	2.1	1.7	11.5	47.3	10.9
5	10.6	14.4	29.8	3.3	14.0	3.6	24.5	1.8	1.9	1.7	30.7	70.5	20.8
10	12.9	17.7	37.1	3.7	13.9	3.6	21.4	1.7	1.5	1.5	41.7	88.5	31.6
15	13.3	17.9	37.8	4.5	13.5	3.3	20.3	1.6	1.3	1.6	58.6	101.5	33.9
20	13.4	18.6	38.6	4.4	13.2	3.6	18.7	1.5	1.5	1.4	62.2	106.5	36.0
20-year outcomes													
1	3.6	3.4	7.2	0.1	3.7	0.6	11.1	0.8	0.3	0.5	-2.2	4.3	-0.9
5	6.0	7.0	14.0	0.6	5.1	0.8	13.0	1.0	0.4	0.8	-3.1	11.2	5.7
10	8.7	9.9	20.4	1.1	6.1	1.2	12.5	1.2	0.3	0.9	0.0	19.8	13.9
15	9.5	10.8	22.9	1.5	6.0	1.1	12.6	1.0	0.3	0.8	3.0	24.9	16.8
20	9.7	11.3	23.8	1.7	6.1	1.2	11.0	1.0	0.3	0.9	2.3	25.3	19.6
10-year outcomes													
1	1.3	0.9	2.2	0.0	0.0	0.0	4.2	0.3	0.1	0.1	-0.6	-0.3	-2.3
5	2.8	2.5	5.5	0.1	0.0	0.0	5.7	0.4	0.2	0.3	-1.6	0.4	-0.5
10	4.5	4.1	8.9	0.1	0.0	0.0	5.3	0.5	0.1	0.3	-1.3	2.4	3.2
15	5.2	4.6	10.3	0.2	0.0	0.0	5.8	0.4	0.1	0.3	-1.0	3.8	4.3
20	4.9	5.2	10.7	0.2	0.0	0.0	5.1	0.5	0.1	0.3	-1.3	3.7	5.3

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Appendix A Table 9. Detailed Benefits and Harms From Aspirin Use for Men Aged 60-69 (KQs 1a-c)

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	13.1	8.2	25.3	2.6	12.1	2.8	34.2	1.3	2.4	1.2	3.9	27.6	4.5
10	14.1	8.4	26.0	2.9	11.2	2.6	32.1	1.6	2.2	1.4	10.9	32.6	6.4
15	16.3	9.9	31.2	3.6	10.4	2.4	30.2	1.2	2.2	1.1	19.0	42.0	13.8
20	17.7	10.3	33.0	4.1	9.0	1.9	27.2	1.4	2.2	1.2	20.7	43.1	17.5
20-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	9.2	5.0	15.5	0.7	7.2	1.2	25.3	1.1	1.0	0.9	-6.3	5.9	-3.0
10	11.5	5.9	19.0	1.2	7.4	1.4	25.4	1.2	1.1	1.0	-4.0	10.1	1.0
15	13.6	7.9	24.5	2.1	7.3	1.5	25.1	1.0	1.3	0.9	0.0	16.8	7.8
20	15.5	8.6	27.5	2.7	6.4	1.0	23.2	1.3	1.5	1.0	-0.5	17.2	12.1
10-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	3.6	1.8	5.6	0.1	0.0	0.0	11.9	0.6	0.4	0.4	-2.4	-1.6	-6.8
10	5.8	2.7	8.8	0.2	0.0	0.0	12.6	0.7	0.3	0.4	-2.6	-0.5	-4.3
15	7.5	3.5	11.6	0.3	0.0	0.0	13.9	0.6	0.4	0.5	-2.7	0.4	-2.6
20	9.1	4.4	14.4	0.4	0.0	0.0	13.3	0.8	0.4	0.6	-3.0	1.1	0.7

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Appendix A Table 10. Detailed Benefits and Harms From Aspirin Use for Women Aged 60-69 (KQs 1a-c)

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	6.5	11.2	20.1	1.7	12.5	3.4	27.7	1.9	2.6	1.7	1.4	30.2	4.7
5	8.1	13.3	25.1	2.5	11.0	2.9	25.1	1.9	2.3	1.7	4.5	38.0	11.6
10	8.8	15.0	28.5	3.1	10.5	2.7	23.4	1.6	2.1	1.4	13.3	48.0	17.1
15	9.7	16.6	31.7	3.9	9.3	2.6	22.1	1.7	2.1	1.5	20.2	56.2	21.1
20	9.9	17.3	33.0	4.4	9.7	2.7	22.0	1.9	2.2	1.6	20.3	57.5	23.2
20-year outcomes													
1	3.6	4.6	8.6	0.2	5.5	0.9	17.0	1.1	0.6	0.8	-3.8	5.2	-3.8
5	5.7	7.8	14.7	0.8	5.9	1.0	17.5	1.3	1.1	1.0	-4.4	10.9	2.6
10	6.9	10.4	19.6	1.4	6.0	1.1	17.6	1.3	1.2	1.1	-3.7	16.7	8.1
15	8.0	12.5	23.6	2.1	5.8	1.3	17.4	1.3	1.3	1.2	-1.1	23.1	12.8
20	7.9	13.5	24.8	2.4	6.2	1.2	17.6	1.5	1.3	1.4	-0.4	25.1	14.3
10-year outcomes													
1	1.0	1.1	2.2	0.0	0.0	0.0	7.2	0.4	0.3	0.2	-2.0	-1.6	-5.4
5	2.7	2.8	5.7	0.0	0.0	0.0	8.4	0.5	0.2	0.3	-2.0	0.2	-3.2
10	3.7	4.9	9.0	0.2	0.0	0.0	9.3	0.7	0.3	0.4	-2.1	2.0	-0.8
15	4.5	6.2	11.6	0.4	0.0	0.0	9.2	0.7	0.3	0.5	-2.3	3.8	2.1
20	4.8	7.1	12.9	0.3	0.0	0.0	9.3	0.9	0.3	0.6	-3.1	4.0	3.0

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Appendix A Table 11. Detailed Benefits and Harms From Aspirin Use for Men Aged 70-79 (KQs 1a-c)

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-	-
10	10.9	7.7	21.9	2.6	7.9	2.1	33.2	1.1	3.5	1.0	-7.9	7.6	-1.9
15	11.5	8.1	22.6	2.3	6.9	1.7	31.4	1.1	3.3	0.9	-8.8	7.3	-0.7
20	11.8	9.0	24.1	2.7	6.7	1.6	31.3	1.2	3.4	1.1	-12.2	5.2	1.0
20-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-	-
10	10.0	6.8	19.2	1.9	6.5	1.6	31.1	1.0	3.2	0.9	-10.9	1.9	-4.5
15	10.6	7.4	20.4	1.9	5.6	1.3	29.7	1.0	3.0	0.8	-10.7	2.8	-2.8
20	11.2	8.1	22.2	2.4	5.9	1.3	30.1	1.2	3.2	1.1	-13.5	1.4	-0.8
10-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-	-
10	5.2	3.1	8.8	0.4	0.0	0.0	19.3	0.6	1.2	0.5	-4.7	-2.5	-10.7
15	6.0	3.5	10.1	0.5	0.0	0.0	19.2	0.5	1.1	0.4	-4.0	-1.8	-9.1
20	7.0	4.4	12.1	0.5	0.0	0.0	20.9	0.8	1.5	0.7	-6.5	-2.9	-9.1

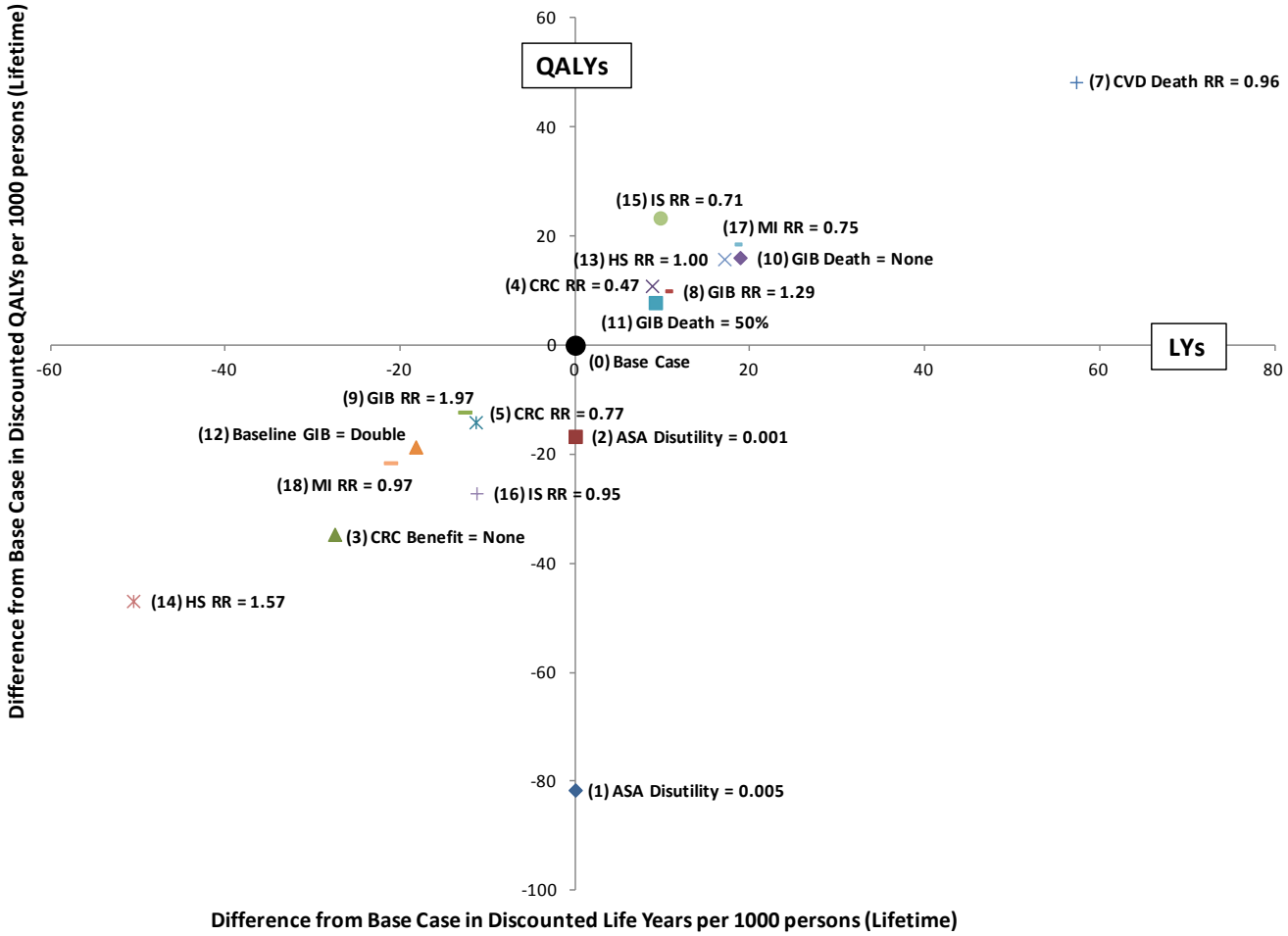
Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Appendix A Table 12. Detailed Benefits and Harms From Aspirin Use for Women Aged 70-79 (KQs 1a-c)

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	5.4	9.7	17.5	1.3	8.4	2.5	27.0	1.5	3.0	1.2	-12.3	9.0	-1.3
10	6.3	10.9	20.2	1.9	7.8	2.3	24.1	1.8	2.8	1.5	-12.7	10.2	4.0
15	6.7	12.4	22.0	2.1	7.3	2.4	23.4	1.5	2.8	1.3	-8.6	15.0	6.5
20	7.7	13.5	24.6	2.4	7.2	2.1	21.9	1.6	2.9	1.6	-13.0	13.9	10.7
20-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	4.3	6.9	12.5	0.6	5.6	1.5	23.3	1.3	2.2	1.0	-11.9	0.9	-5.9
10	5.4	8.8	16.2	1.3	5.6	1.6	21.3	1.5	2.3	1.3	-13.1	3.3	0.3
15	5.8	10.3	18.0	1.5	5.5	1.7	21.1	1.5	2.4	1.2	-12.7	5.6	2.4
20	7.0	12.0	21.7	1.8	5.8	1.5	20.1	1.5	2.6	1.5	-14.4	7.4	7.7
10-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	1.9	2.2	4.2	0.0	0.0	0.0	12.5	0.6	0.4	0.4	-2.8	-1.9	-8.9
10	3.0	3.9	7.3	0.2	0.0	0.0	12.2	0.8	0.7	0.5	-3.5	-0.7	-5.5
15	3.3	5.1	8.8	0.2	0.0	0.0	12.5	0.8	0.9	0.5	-4.4	-0.5	-4.3
20	3.8	6.6	11.3	0.5	0.0	0.0	12.1	0.9	1.1	0.7	-5.6	0.2	-1.2

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Appendix A Figure 1. Comparisons in Lifetime Net Benefit From Taking Aspirin Averaged Across All Age, Sex, and Baseline CVD Risk Groups (KQs 1a-c, Deterministic Sensitivity)



Notes: ASA=acetylsalicylic acid (aspirin); CRC=colorectal cancer; RR=relative risk; CVD=cardiovascular disease; GIB=gastrointestinal bleeding; HS=hemorrhagic stroke; IS=ischemic stroke; MI=myocardial infarction; QALYs=quality-adjusted life years; LYs=life years. Results reflect the difference (sensitivity) in lifetime net outcomes compared to the base case analysis, averaged across all age, sex, and baseline CVD groups. Each numbered item represents a one-way sensitivity analysis with the parameter changed as described. Case (4) CRC Benefit = None is equivalent to setting the CRC RR = 1. Case (10) GIB Death = None is equivalent to setting the case-fatality rates from GI bleeding to 0%. Case (12) Baseline GIB = Double is equivalent to doubling the baseline probabilities of GI bleeding. See Table 1 in report for additional detail. Case (6) CVD Death RR = 0.84 has been excluded from this figure for improved readability.

Appendix A Table 13. Comparisons in Lifetime Net Benefit From Taking Aspirin for Men and Women at 10% CVD Risk (KQ 1a, Deterministic Sensitivity)

	Age 40-49				Age 50-59				Age 60-69				Age 70-79			
	Men		Women		Men		Women		Men		Women		Men		Women	
	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY
	Net Life Years/QALYs per 1000 persons															
(0) Base Case	79.7	109.7	77.5	122.1	46.5	75.1	41.7	88.5	10.9	32.6	13.3	48.0	-7.9	7.6	-12.7	10.2
(1) ASA Disutility = 0.005	79.7	12.8	77.5	7.2	46.5	-3.2	41.7	0.8	10.9	-33.0	13.3	-24.5	-7.9	-43.4	-12.7	-51.8
(2) ASA Disutility = 0.001	79.7	89.7	77.5	99.0	46.5	59.0	41.7	70.5	10.9	18.9	13.3	33.2	-7.9	-2.9	-12.7	-2.6
(3) CRC Benefit = None	38.0	59.1	26.6	63.5	17.5	37.7	6.7	45.0	-8.5	5.8	-7.7	20.1	-16.3	-6.0	-23.1	-5.4
(4) CRC RR = 0.47	90.4	123.3	91.5	138.6	56.1	87.3	51.7	100.9	16.5	40.4	19.9	56.2	-4.0	12.9	-7.6	16.6
(5) CRC RR = 0.77	63.1	89.4	57.5	99.2	34.6	59.7	28.5	71.7	2.1	21.2	4.5	36.7	-12.1	1.9	-17.9	3.4
(6) CVD Death RR = 0.84	368.4	354.6	362.0	360.2	315.9	303.2	298.1	303.1	219.4	209.0	222.5	222.9	139.5	132.2	132.0	132.0
(7) CVD Death RR = 0.96	148.6	168.3	150.5	183.5	105.7	125.3	106.4	142.8	60.9	74.8	68.0	93.9	28.5	38.5	26.8	43.6
(8) GIB RR = 1.29	86.5	116.7	87.0	131.3	56.3	84.9	50.9	97.2	21.0	42.6	23.0	57.4	6.1	21.0	0.0	22.1
(9) GIB RR = 1.97	70.5	100.4	67.5	112.3	35.7	64.3	32.5	79.2	-5.4	16.9	0.5	35.8	-25.7	-9.2	-29.6	-5.5
(10) GIB Death = None	93.3	121.3	92.7	135.0	63.2	89.4	57.0	101.4	28.9	48.0	33.2	65.1	18.4	30.1	10.4	29.9
(11) GIB Death = 50%	87.5	116.3	84.2	127.8	54.9	82.4	49.4	95.0	19.9	40.3	23.4	56.7	4.5	18.2	-2.4	19.0
(12) Baseline GIB = Double	68.4	97.1	66.2	109.8	31.2	58.5	25.7	71.9	-10.6	10.7	-6.1	28.8	-33.4	-17.4	-39.6	-15.3
(13) HS RR = 1.00	96.7	125.1	99.3	142.5	60.7	88.2	65.7	110.3	26.1	46.8	30.9	64.5	1.0	16.0	1.5	23.6
(14) HS RR = 1.57	32.8	66.6	8.2	58.1	-6.3	26.7	-23.7	28.0	-35.8	-10.6	-42.5	-4.1	-32.6	-15.3	-55.4	-30.4
(15) IS RR = 0.71	91.0	133.8	93.1	159.9	54.3	93.4	57.0	125.0	15.1	45.7	23.8	75.2	-4.5	16.5	-7.4	25.0
(16) IS RR = 0.95	66.3	81.3	55.9	75.2	36.1	51.3	27.5	48.5	4.1	16.4	1.9	17.8	-12.1	-2.9	-17.5	-5.8
(17) MI RR = 0.75	116.0	145.9	103.8	148.3	71.4	100.5	63.2	109.9	24.5	46.7	22.9	58.3	-2.2	14.1	-9.4	14.4
(18) MI RR = 0.97	35.1	65.8	46.2	90.9	16.6	44.8	21.1	66.8	-4.1	17.3	1.4	34.9	-17.5	-2.5	-17.6	4.5

Notes: ASA=acetylsalicylic acid (aspirin); CRC=colorectal cancer; RR=relative risk; CVD=cardiovascular disease; GIB=gastrointestinal bleeding; HS=hemorrhagic stroke; IS=ischemic stroke; MI=myocardial infarction; QALYs=quality-adjusted life years; LYs=life years. Results reflect the difference (sensitivity) in lifetime net outcomes compared to the base case analysis, averaged across all age, sex, and baseline CVD groups. Each numbered item represents a one-way sensitivity analysis with the parameter changed as described. Case (4) CRC Benefit = None is equivalent to setting the CRC RR = 1. Case (10) GIB Death = None is equivalent to setting the case-fatality rates from GI bleeding to 0%. Case (12) Baseline GIB = Double is equivalent to doubling the baseline probabilities of GI bleeding. See Table 1 for additional detail.

Appendix A Table 14. Comparisons in Net Benefit From Taking Aspirin Over 20 Years for Men and Women at 10% CVD Risk (KQ 1b, Deterministic Sensitivity)

	Age 40-49				Age 50-59				Age 60-69				Age 70-79			
	Men		Women		Men		Women		Men		Women		Men		Women	
	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY
	Net Life Years/QALYs per 1000 persons															
(0) Base Case	0.7	12.7	1.1	13.1	1.8	16.8	0.0	19.8	-4.0	10.1	-3.7	16.7	-10.9	1.9	-13.1	3.3
(1) ASA Disutility = 0.005	0.7	-56.4	1.1	-60.7	1.8	-46.1	0.0	-46.4	-4.0	-47.5	-3.7	-44.0	-10.9	-46.6	-13.1	-53.1
(2) ASA Disutility = 0.001	0.7	-1.2	1.1	-1.7	1.8	4.1	0.0	6.5	-4.0	-1.8	-3.7	4.5	-10.9	-8.1	-13.1	-8.2
(3) CRC Benefit = None	-1.8	6.6	-1.7	7.4	-1.8	8.2	-4.1	11.2	-8.4	0.1	-7.9	7.9	-15.0	-6.7	-17.5	-4.9
(4) CRC RR = 0.47	1.5	14.5	1.6	14.4	3.4	19.9	0.9	22.5	-2.7	13.0	-2.5	19.1	-9.0	5.1	-11.0	6.5
(5) CRC RR = 0.77	-0.4	10.1	-0.2	10.5	0.2	13.0	-1.7	16.2	-6.1	5.9	-5.3	13.3	-13.0	-1.7	-15.3	-0.3
(6) CVD Death RR = 0.84	68.7	71.3	53.5	58.0	107.5	107.2	86.6	93.5	112.5	109.1	99.7	104.1	103.6	99.0	87.5	88.3
(7) CVD Death RR = 0.96	16.4	26.2	15.3	25.3	24.3	36.0	23.6	39.9	25.5	35.1	24.0	40.2	17.0	25.6	13.4	25.8
(8) GIB RR = 1.29	1.3	13.7	1.8	14.0	4.2	19.6	1.0	21.3	-1.0	13.7	-0.5	20.3	-1.0	11.7	-4.9	11.2
(9) GIB RR = 1.97	0.2	11.6	0.4	12.1	0.0	14.3	-1.3	18.1	-10.0	3.5	-7.8	12.2	-24.1	-10.9	-24.0	-7.2
(10) GIB Death = None	2.2	14.0	1.9	13.8	5.7	20.2	2.4	22.0	2.2	15.4	3.0	22.5	8.0	18.2	1.4	15.6
(11) GIB Death = 50%	1.7	13.5	1.4	13.3	4.0	18.7	1.4	21.1	-1.2	12.5	-0.4	19.6	-1.9	9.6	-6.9	8.5
(12) Baseline GIB = Double	0.6	11.5	0.6	12.0	-2.2	11.7	-3.3	16.0	-13.1	-0.1	-9.4	10.3	-29.5	-16.9	-31.4	-14.5
(13) HS RR = 1.00	4.4	16.4	3.5	16.2	7.2	22.2	7.0	27.1	3.7	17.7	4.7	25.2	-4.6	8.0	-3.5	12.7
(14) HS RR = 1.57	-9.3	1.9	-8.3	2.0	-17.7	-2.9	-19.2	-0.6	-28.3	-13.7	-28.8	-8.6	-29.6	-15.9	-40.8	-24.3
(15) IS RR = 0.71	1.3	17.3	1.6	18.9	3.0	22.6	1.6	30.0	-3.5	16.1	-2.0	28.4	-9.7	7.6	-11.1	12.2
(16) IS RR = 0.95	0.2	7.5	0.9	6.5	0.2	9.1	-1.5	7.8	-5.5	2.7	-6.1	3.2	-13.2	-5.6	-15.3	-7.0
(17) MI RR = 0.75	2.1	16.0	2.1	15.0	5.8	22.3	1.9	22.9	-0.5	14.6	-1.9	19.4	-7.9	5.9	-11.7	5.5
(18) MI RR = 0.97	-1.6	8.4	0.4	11.2	-2.1	10.8	-2.4	16.1	-7.8	5.1	-6.3	12.6	-15.9	-4.1	-15.4	0.1

Notes: ASA=acetylsalicylic acid (aspirin); CRC=colorectal cancer; RR=relative risk; CVD=cardiovascular disease; GIB=gastrointestinal bleeding; HS=hemorrhagic stroke; IS=ischemic stroke; MI=myocardial infarction; QALYs=quality-adjusted life years; LYs=life years. Results reflect the difference (sensitivity) in lifetime net outcomes compared to the base case analysis, averaged across all age, sex, and baseline CVD groups. Each numbered item represents a one-way sensitivity analysis with the parameter changed as described. Case (4) CRC Benefit = None is equivalent to setting the CRC RR = 1. Case (10) GIB Death = None is equivalent to setting the case-fatality rates from GI bleeding to 0%. Case (12) Baseline GIB = Double is equivalent to doubling the baseline probabilities of GI bleeding. See Table 1 for additional detail.

Appendix A Table 15. Comparisons in Net Benefit From Taking Aspirin Over 10 Years for Men and Women at 10% CVD Risk (KQ 1c, Deterministic Sensitivity)

	Age 40-49				Age 50-59				Age 60-69				Age 70-79			
	Men		Women		Men		Women		Men		Women		Men		Women	
	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY	LY	QALY
	Net Life Years/QALYs per 1000 persons															
(0) Base Case	-0.7	1.4	-0.3	1.8	-1.3	1.3	-1.3	2.4	-2.6	-0.5	-2.1	2.0	-4.7	-2.5	-3.5	-0.7
(1) ASA Disutility = 0.005	-0.7	-38.2	-0.3	-39.0	-1.3	-37.0	-1.3	-36.6	-2.6	-37.6	-2.1	-35.7	-4.7	-37.0	-3.5	-37.5
(2) ASA Disutility = 0.001	-0.7	-6.5	-0.3	-6.4	-1.3	-6.4	-1.3	-5.4	-2.6	-8.0	-2.1	-5.6	-4.7	-9.4	-3.5	-8.1
(3) CRC Benefit = None	-0.7	1.4	-0.3	1.8	-1.3	1.3	-1.3	2.5	-2.6	-0.5	-2.1	1.9	-4.7	-2.6	-3.5	-0.8
(4) CRC RR = 0.47	-0.7	1.4	-0.3	1.8	-1.3	1.3	-1.3	2.5	-2.6	-0.5	-2.1	1.9	-4.7	-2.6	-3.5	-0.8
(5) CRC RR = 0.77	-0.7	1.4	-0.3	1.8	-1.3	1.3	-1.3	2.5	-2.6	-0.5	-2.1	1.9	-4.7	-2.6	-3.5	-0.8
(6) CVD Death RR = 0.84	14.5	14.5	11.3	11.8	25.0	23.9	20.1	20.8	29.8	27.1	24.7	24.7	30.6	27.6	23.7	22.5
(7) CVD Death RR = 0.96	2.6	4.2	2.9	4.6	3.8	5.7	5.5	8.2	6.0	6.7	5.0	8.0	3.7	4.6	3.4	5.2
(8) GIB RR = 1.29	-0.5	1.7	-0.3	1.9	-0.9	2.0	-1.1	2.8	-1.7	0.7	-1.5	2.8	-2.6	0.0	-2.1	0.9
(9) GIB RR = 1.97	-0.7	1.1	-0.4	1.6	-1.7	0.5	-1.5	2.0	-4.0	-2.5	-2.8	0.8	-7.5	-5.9	-5.5	-3.2
(10) GIB Death = None	-0.3	1.7	-0.3	1.8	-0.7	1.8	-0.8	2.9	-1.0	0.8	-0.9	3.0	-0.8	0.8	-1.3	1.1
(11) GIB Death = 50%	-0.5	1.6	-0.3	1.8	-1.0	1.5	-1.1	2.7	-1.9	0.1	-1.4	2.5	-2.9	-1.0	-2.7	0.0
(12) Baseline GIB = Double	-0.5	1.2	-0.4	1.5	-2.6	-0.6	-2.1	1.3	-4.7	-3.5	-3.0	0.5	-8.3	-7.1	-6.5	-4.3
(13) HS RR = 1.00	-0.1	2.2	0.0	2.4	-0.4	2.5	-0.1	4.0	-1.2	1.1	-0.6	3.8	-3.2	-0.9	-1.9	1.3
(14) HS RR = 1.57	-2.3	-0.9	-1.6	-0.3	-4.8	-3.2	-4.7	-2.4	-7.7	-6.6	-7.2	-4.5	-9.4	-7.8	-9.5	-7.9
(15) IS RR = 0.71	-0.7	2.3	-0.3	3.0	-1.3	2.6	-1.2	4.9	-2.5	1.0	-2.0	5.0	-4.7	-1.2	-3.4	1.2
(16) IS RR = 0.95	-0.7	0.3	-0.3	0.3	-1.5	-0.6	-1.4	-0.4	-2.7	-2.4	-2.2	-1.4	-4.8	-4.4	-3.7	-3.1
(17) MI RR = 0.75	-0.6	2.1	-0.2	2.2	-1.0	2.2	-1.2	3.0	-2.4	0.2	-2.0	2.4	-4.4	-1.7	-3.4	-0.4
(18) MI RR = 0.97	-0.8	0.4	-0.4	1.3	-1.4	0.3	-1.5	1.7	-2.8	-1.4	-2.3	1.1	-5.1	-3.5	-3.7	-1.3

Notes: ASA=acetylsalicylic acid (aspirin); CRC=colorectal cancer; RR=relative risk; CVD=cardiovascular disease; GIB=gastrointestinal bleeding; HS=hemorrhagic stroke; IS=ischemic stroke; MI=myocardial infarction; QALYs=quality-adjusted life years; LYs=life years. Results reflect the difference (sensitivity) in lifetime net outcomes compared to the base case analysis, averaged across all age, sex, and baseline CVD groups. Each numbered item represents a one-way sensitivity analysis with the parameter changed as described. Case (4) CRC Benefit = None is equivalent to setting the CRC RR = 1. Case (10) GIB Death = None is equivalent to setting the case-fatality rates from GI bleeding to 0%. Case (12) Baseline GIB = Double is equivalent to doubling the baseline probabilities of GI bleeding. See Table 1 for additional detail.

Appendix A Table 16. Marginal Discounted Lifetime Net Benefit From Taking Aspirin Now Versus Delaying 10 Years (KQ 2)

10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69
Men			
	Discounted Net Life Years per 1000 persons (95% Confidence Interval)		
1	4.8 (2.7 to 6.9)	4.8 (2.7 to 6.8)	N/A
5	9.5 (7.3 to 11.7)	7.1 (4.6 to 9.7)	2.5 (0.0 to 5.0)
10	11.4 (8.6 to 14.2)	12.3 (9.4 to 15.3)	5.9 (3.2 to 8.6)
15	15.1 (12.2 to 17.9)	13.8 (10.8 to 16.7)	8.9 (6.1 to 11.7)
20	17.2 (14.5 to 19.9)	20.2 (16.9 to 23.4)	8.9 (5.8 to 12.1)
	Discounted QALYs per 1000 persons (95% Confidence Interval)		
1	6.3 (4.3 to 8.3)	7.8 (5.9 to 9.8)	N/A
5	13.4 (11.3 to 15.5)	12.1 (9.7 to 14.5)	8.7 (6.3 to 11.0)
10	17.1 (14.4 to 19.8)	19.7 (16.9 to 22.5)	12.9 (10.3 to 15.5)
15	20.8 (18.0 to 23.6)	21.3 (18.5 to 24.1)	17.0 (14.3 to 19.7)
20	23.4 (20.8 to 26.1)	29.3 (26.1 to 32.4)	17.9 (15.0 to 20.9)
Women			
	Discounted Net Life Years per 1000 persons (95% Confidence Interval)		
1	3.7 (1.9 to 5.4)	3.1 (1.0 to 5.1)	4.0 (1.6 to 6.3)
5	9.1 (6.6 to 11.6)	6.2 (3.2 to 9.2)	5.9 (3.2 to 8.5)
10	11.5 (9.0 to 14.0)	11.2 (8.3 to 14.0)	6.8 (3.9 to 9.7)
15	12.8 (10.1 to 15.5)	14.3 (11.2 to 17.5)	10.1 (7.0 to 13.1)
20	10.7 (8.3 to 13.2)	15.2 (12.0 to 18.4)	9.7 (6.5 to 12.8)
	Discounted QALYs per 1000 persons (95% Confidence Interval)		
1	5.9 (4.2 to 7.7)	6.4 (4.4 to 8.4)	8.1 (5.9 to 10.3)
5	14.0 (11.5 to 16.5)	13.6 (10.8 to 16.5)	13.4 (10.8 to 16.0)
10	18.3 (15.8 to 20.8)	21.9 (19.0 to 24.7)	17.4 (14.5 to 20.3)
15	20.1 (17.4 to 22.7)	25.9 (22.8 to 29.0)	22.9 (19.9 to 25.9)
20	18.6 (16.2 to 21.0)	26.4 (23.3 to 29.5)	23.3 (20.3 to 26.4)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference in net benefit from starting aspirin at model baseline/initiation versus waiting 10 years. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample. Results in this table are discounted to present value using a 3% discount rate.

Appendix A Table 17. Comparison of Modeled Baseline (Preventable) 10-Year Event Rates to 2009 USPSTF Review

	USPSTF 2009		This study			
	MI	Stroke	Total ASCVD events	Non-fatal MI	Non-fatal IS	CVD deaths
	Events over 10 years per 1000 persons at 10% 10-year CHD/stroke/ASCVD risk					
Men						
Age 40-49	100		90	53	10	27
Age 50-59	100		111	53	15	43
Age 60-69	100		114	43	16	55
Age 70-79	100		130	40	18	72
Women						
Age 40-49		100	56	25	13	18
Age 50-59		100	93	32	25	36
Age 60-69		100	105	28	30	47
Age 70-79		100	95	21	24	50

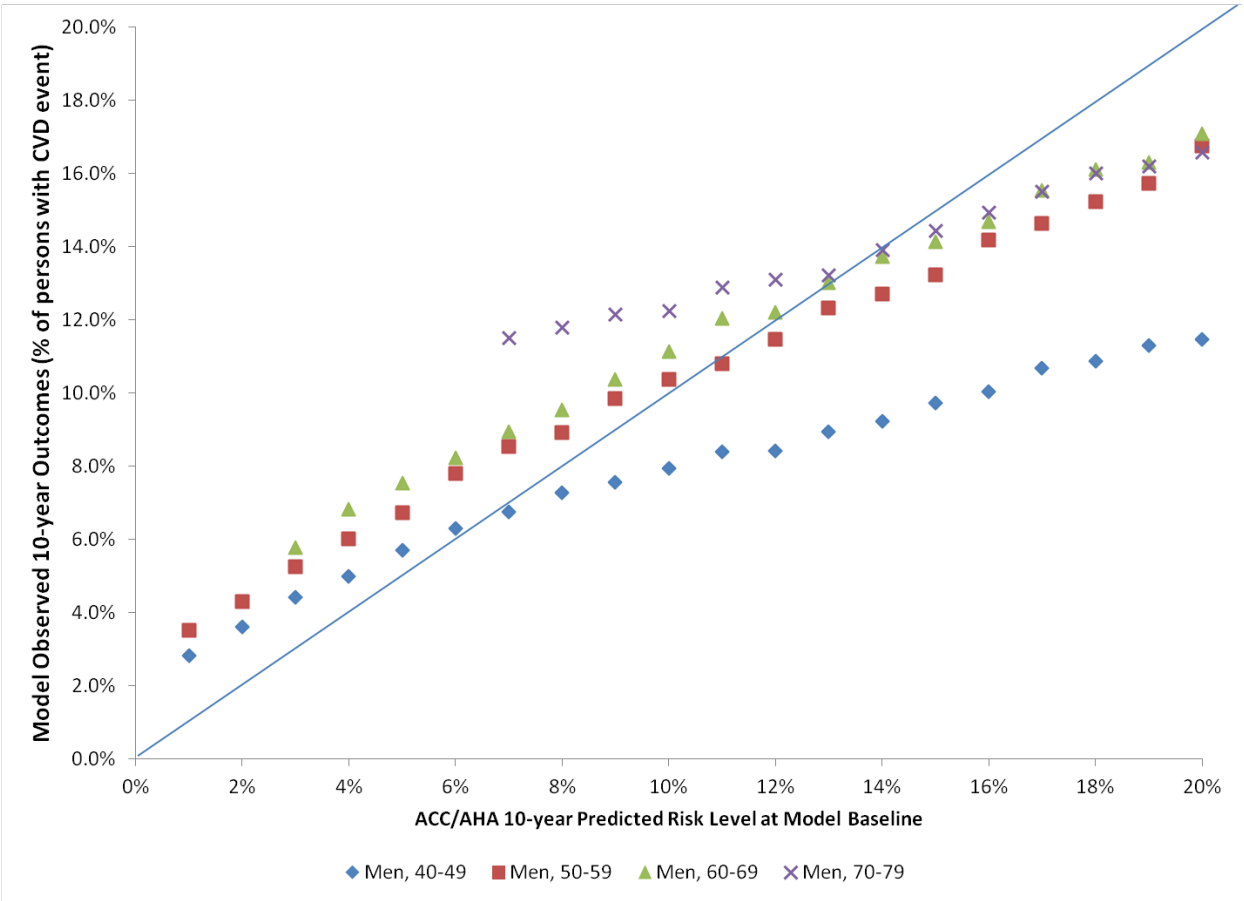
Notes: MI=myocardial infarction; ASCVD=atherosclerotic cardiovascular disease (non-fatal MI, non-fatal stroke, or coronary death); IS=ischemic stroke; CVD=cardiovascular disease; CHD=coronary heart disease. The USPSTF 2009 columns refer to the predicted baseline (i.e., preventable) event rates used in the 2009 USPSTF recommendation statement on aspirin [1]. The first column refers to the number of first MIs expected over 10 years in 1,000 men with 10% 10-year CHD risk. The second column refers to the number of first strokes (hemorrhagic and ischemic) expected over 10 years in 1,000 women with 10% 10-year stroke risk. The remaining columns refer to the number of preventable events predicted by the model in this study for 1,000 persons with 10% 10-year ACC/AHA ASCVD risk [2] among the no-aspirin (i.e., baseline) groups. In these columns, the number of non-fatal events do not necessarily correlate with the number of persons (i.e., a single person could have multiple non-fatal MIs over the 10 year period).

Appendix A Table 18. Comparison of Modeled Baseline GI Bleeding and Hemorrhagic Stroke Event Rates

	GI Bleeds		Hemorrhagic Strokes		
	USPSTF 2009	This Study	USPSTF 2009	This Study	Cohort Studies
	Events per 1000 person-years				
Men					
Age 40-49	0.8	0.5	0.15	0.18	
Age 45-54					0.22
Age 50-59	0.8	1.2	0.15	0.32	
Age 55-64					0.45
Age 60-69	2.4	2.1	0.15	0.54	
Age 65-64					1.12
Age 70-79	3.6	3.9	0.15	0.70	
Women					
Age 40-49	0.4	0.3	N/R	0.12	
Age 45-54					0.18
Age 50-59	0.4	0.7	N/R	0.31	
Age 55-64					0.35
Age 60-69	1.2	1.3	N/R	0.50	
Age 65-64					0.75
Age 70-79	1.8	2.3	N/R	0.74	

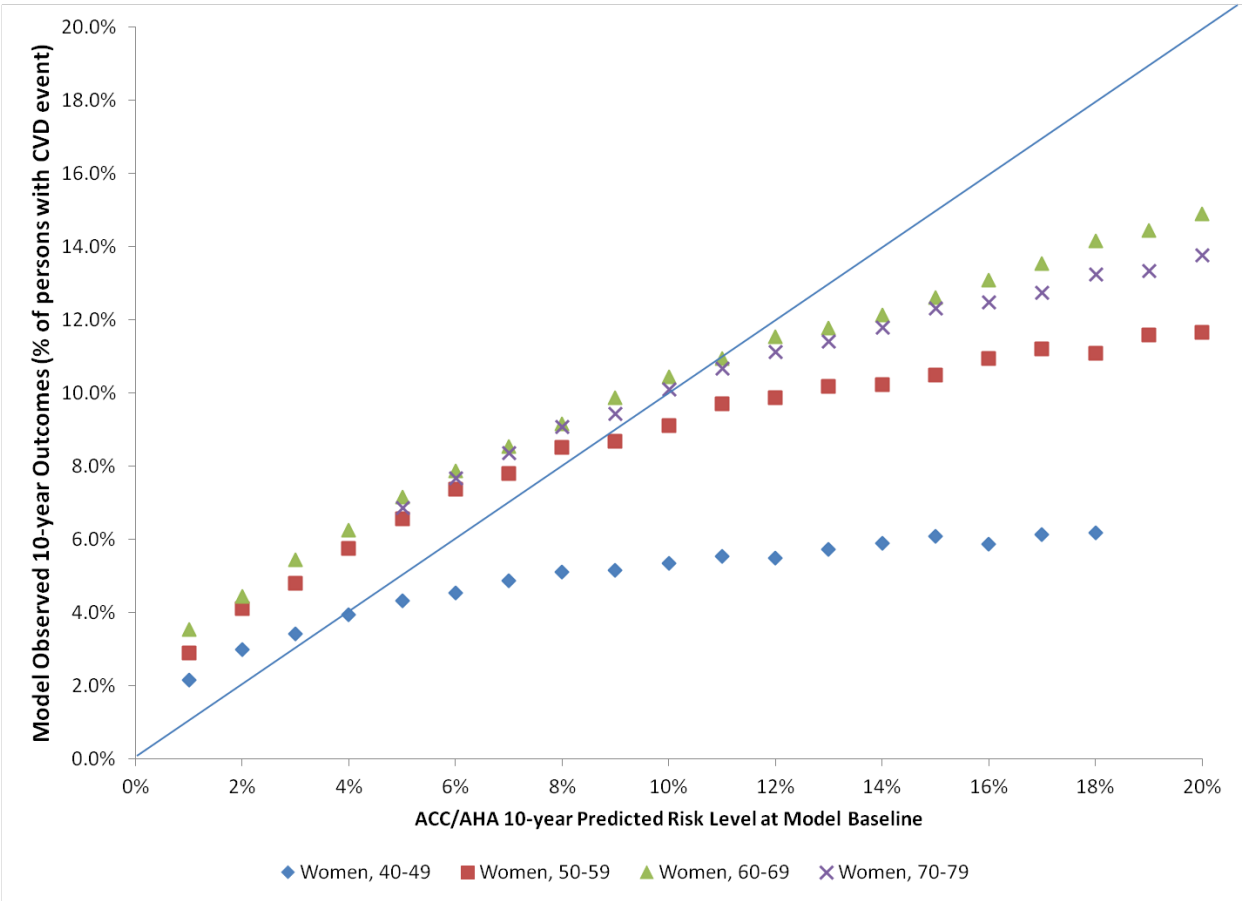
Notes: GI=gastrointestinal; N/R=not reported. The 2009 USPSTF columns refer the baseline GI bleeding and hemorrhagic stroke rates underlying Figures 2 and 4 in the 2009 USPSTF recommendation statement on aspirin [1]. These GI bleeding rates are sourced from an analysis of population-based databases in the United Kingdom and Spain [3], and the baseline hemorrhagic stroke rates are inferred from the excess rate reported in Figure 2 of the recommendation statement and the 1.69 relative risk for hemorrhagic stroke found by the supporting evidence review [4]. The baseline population GI bleed rates used in this study are derived from a population-based study conducted in Italy [5], with age and sex adjustments made for the U.S. population. Hemorrhagic stroke rates from this study are generated by a risk equation derived from Framingham Heart Study data specifically for the model. Hemorrhagic stroke rates are presented for the approximate median baseline ACC/AHA 10-year CVD risk in the U.S. population for men and women aged 40-69 (specifically, these were 3% for men aged 40-49, 7% for men aged 50-59, 15% for men aged 60-69, 1% for women aged 40-49, 3% for women aged 50-59, and 8% for women aged 60-69). We found median baseline ACC/AHA 10-year CVD risk to be higher than 20% for men and women aged 70-79, but for these ages, persons at 20% risk are presented (i.e., the highest CVD risk level considered in our analysis). The last column includes estimated hemorrhagic stroke rates from major cohort studies—including, the Atherosclerosis Risk in Communities (ARIC) study, Cardiovascular Health Study (CHS), Framingham Heart Study (FHS), and Strong Heart Study—as reported by the National Institutes of Health [6]. Hemorrhagic stroke rates were estimated using the 13% share of hemorrhagic-to-total strokes reported in [7]. Event rates from all three studies combined for the age 45-54 estimates—ARIC, FHS, and SHS—were deemed "unreliable" as reported individually. Not presented in the table, a population-based study within Greater Cincinnati/Northern Kentucky also reports age and sex-adjusted rates for first-ever hospital-ascertained stroke to be 0.41 per 1,000 persons in 2005 [8].

Appendix A Figure 2. Comparison of 10-Year Model Outcomes With ACC/AHA 10-Year Risk Among Men Aged 40-79 Years



Notes: ACC/AHA=American College of Cardiology/American Heart Association. The y-axis represents the percent of persons observed having their first hard atherosclerotic cardiovascular disease (ASCVD) event (non-fatal MI, non-fatal stroke, or coronary death) in a ModelHealth: CVD simulated cohort with a 10-year ACC/AHA baseline risk specified in x-axis [2]. The 45-degree line indicates perfect concordance in 10-year outcomes predicted by the ACC/AHA risk calculator and those observed in a simulated population. Points above the 45-degree line indicate that 10-year event rates simulated in the model are above the rate indicated by 10-year ACC/AHA risk; points below the 45-degree line indicate that 10-year event rates simulated in the model are below the rate indicated by 10-year ACC/AHA risk. Similar patterns have been seen in other comparisons [9-12].

Appendix A Figure 3. Comparison of 10-Year Model Outcomes With ACC/AHA 10-Year Risk Among Women Aged 40-79 Years



Notes: ACC/AHA=American College of Cardiology/American Heart Association. The y-axis represents the percent of persons observed having their first hard atherosclerotic cardiovascular disease (ASCVD) event (non-fatal MI, non-fatal stroke, or coronary death) in a ModelHealth: CVD simulated cohort with a 10-year ACC/AHA baseline risk specified in x-axis [2]. The 45-degree line indicates perfect concordance in 10-year outcomes predicted by the ACC/AHA risk calculator and those observed in a simulated population. Points above the 45-degree line indicate that 10-year event rates simulated in the model are above the rate indicated by 10-year ACC/AHA risk; points below the 45-degree line indicate that 10-year event rates simulated in the model are below the rate indicated by 10-year ACC/AHA risk. Similar patterns have been seen in other comparisons [9-12].

Appendix A Table 19. Comparison of Positive Net Event Thresholds by CVD Risk Over a 10-Year Horizon to 2009 USPSTF Review

	2009 USPSTF	This Study
	Positive net event threshold (% 10-year CVD risk)	
Men		
Age 40-49		4%
Age 45-59	4%	
Age 50-59		9%
Age 60-69	9%	19%
Age 70-79	12%	>20%
Women		
Age 40-49		3%
Age 50-59		6%
Age 55-59	3%	
Age 60-69	8%	12%
Age 70-79	11%	>20%

Notes: The 2009 USPSTF column refers to the level of 10-year coronary heart disease risk for men and 10-year stroke risk for women for which expected the number of prevented CVD events (i.e., benefits) are expected to exceed the number of excess bleeding events (i.e., harms) over 10 years of using aspirin for primary prevention, as described in Figure 3 of the 2009 USPSTF recommendation statement on aspirin [1]. Thresholds from the results of this study were identified as the level of baseline 10-year CVD risk for which the average net events over 10 years is positive at that and at all CVD risk levels considered above it. Positive net event thresholds that were not identified in this study are described as >20% in the table, and it is important to note that a CVD risk threshold for positive net events over 10 years may not exist at *any* CVD risk level for such cases.

Appendix A Table 20. Comparison of Major Event Rates to van Kruijsdijk et al (2015)

	Major CVD	CRC	Major GI Bleeding
	Net events per 1000 persons		
Women, Mean Age = 54.7, 10 Years (van Kruijsdijk et al. [13])	-1.8	-0.1†	+5.0
Women, Mean Age = 54.7, 15 Years (van Kruijsdijk et al. [13])	-2.7	-1.4	+7.5
Women, Age 50-59, 1% CVD Risk, 10 Years (This Study)	-1.9	-	+4.2
Women, Age 50-59, 1% CVD Risk, 20 Years (This Study)	-6.3	-3.7	+11.1
Women, Age >= 65, 10 Years (van Kruijsdijk et al. [13])	-21.4	+2.7†	+11.2
Women, Age >= 65, 15 Years (van Kruijsdijk et al. [13])	-31.1	+1.1†	+16.6
Women, Age 70-79, 10% CVD Risk, 10 Years (This Study)	-6.3	-	+12.2
Women, Age 70-79, 10% CVD Risk, 20 Years (This Study)	-14.0	-5.6	+21.3

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal. Major CVD events include non-fatal myocardial infarction, non-fatal ischemic and hemorrhagic stroke, and CVD-related death. Major CVD and incident CRC events are net prevented and major GI bleeding events are net excess due to aspirin. The symbol † indicates that 95% confidence interval for the finding included zero. Event rates were not tabulated over 15 years in this study, but 10- and 20- year outcomes are provided to give context for an approximate 15-year comparison. The CVD risk thresholds chosen for comparison to this study were approximated based on the baseline population characteristics reported in van Kruijsdijk et al. [13].

Appendix A Table 21. Comparison of Major Event Rates to Cuzick et al (2015)

	MI	Stroke	Major Bleeding
	Net events per 1000 persons over 10 years		
Men, Age 55 (Cuzick et al. [14])	6.8	0.8	4.9
Men, Age 50-59, 8% CVD Risk (This Study)	5.9	1.6	9.1
Men, Age 65 (Cuzick et al. [14])	11.5	1.8	8.1
Men, Age 60-69, 15% CVD Risk (This Study)	7.5	2.9	13.9
Women, Age 55 (Cuzick et al. [14])	2.3	0.7	2.5
Women, Age 50-59, 4% CVD Risk (This Study)	2.8	1.6	4.8
Women, Age 65 (Cuzick et al. [14])	6.1	1.5	4.3
Women, Age 60-69, 9% CVD Risk (This Study)	3.5	4.3	9.0

Notes: MI=myocardial infarction; CVD=cardiovascular disease. MI and stroke events are net prevented and major bleeding events are net excess due to aspirin. Stroke estimates from the this study model include the net of ischemic and hemorrhagic stroke; Cuzick et al. [14] do not clarify their stroke definition, but they likely also used a combined measure. Major bleeding was defined as major GI bleeding in this study's results and as major extracranial bleeding in the Cuzick et al. [14] results. Cuzick et al. [14] use United Kingdom data for baseline population incidence rates; approximate US population mean baseline CVD risk for each respective group was used for the comparison this study.

Appendix A Table 22. Comparison of CVD and CRC Mortality Rates in Model Results Versus Clinical Trials

	RR	95% CI
CVD mortality over 10 years for persons at 10% baseline CVD risk		
Model results		
Men, aged 40-49	0.997	(0.95 to 1.05)
Men, aged 50-59	0.996	(0.95 to 1.04)
Men, aged 60-69	0.997	(0.96 to 1.03)
Men, aged 70-79	0.995	(0.96 to 1.03)
Women, aged 40-49	0.999	(0.94 to 1.07)
Women, aged 50-59	0.997	(0.95 to 1.04)
Women, aged 60-69	0.995	(0.96 to 1.04)
Women, aged 70-79	0.996	(0.96 to 1.04)
Clinical trial results [15]	0.96	(0.84 to 1.11)
CRC mortality over 20 years for persons at 10% baseline CVD risk		
Model results		
Men, aged 40-49	0.76	(0.65 to 0.89)
Men, aged 50-59	0.78	(0.69 to 0.89)
Men, aged 60-69	0.82	(0.73 to 0.91)
Men, aged 70-79	0.86	(0.79 to 0.94)
Women, aged 40-49	0.73	(0.61 to 0.88)
Women, aged 50-59	0.75	(0.66 to 0.86)
Women, aged 60-69	0.82	(0.72 to 0.92)
Women, aged 70-79	0.81	(0.73 to 0.90)
Clinical trial results [16]	0.67	(0.52 to 0.86)

Notes: RR=relative risk; CI=confidence interval; CVD=cardiovascular disease; CRC=colorectal cancer.

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HealthPartners Institute for Education and Research ModelHealth™: Cardiovascular Disease

1 Model Overview

The decision analysis of aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in this study was conducted using an adapted version of the HealthPartners Institute for Education and Research ModelHealth™: Cardiovascular disease microsimulation model. Adaptations for this analysis include a full integration of detailed tobacco use functions from the ModelHealth™: Tobacco microsimulation model, and the addition of four categories of cancer aligning with those considered by the systematic evidence reviews that were conducted in parallel with this study [1, 2]. The final analysis reflects only the inclusion of CRC, based on the systematic evidence review's findings, which lacked support for a significant effect of aspirin on the other cancer types. Herein, the adapted model used for this study is referred to as ModelHealth: CVD.

ModelHealth: CVD is a collection of scientific evidence-based parameters, mathematical functions, and procedural logic—implemented using Visual Basic 6 and Microsoft Excel—designed to evaluate cardiovascular disease prevention policies at the population level. The primary unit of observation in this model is an individual representative person who takes on a variety of detailed attributes (such as age, sex, race/ethnicity, BMI, systolic blood pressure, disease status, etc.). The lifetime progression of these characteristics is simulated over time. Epidemiological data sourced from the Framingham Heart Study—a major cardiovascular disease surveillance study ongoing since 1948—plays an important role in this model's construction.

Although the mechanics of ModelHealth: CVD center on individuals—i.e., through microsimulation—policy relevance is achieved through aggregating a sufficient number of individuals to be representative of a policy-relevant group, such as the U.S. population. ModelHealth: CVD can be scaled easily to simulate the lifetime progression of hundreds, thousands, or even millions of individuals. Policy interventions are evaluated by simulating the same population twice—once with the policy intervention of interest, such as a clinical preventive service, imposed, and once without it. In practice, this evaluation approach is comparable to a randomized clinical trial (RCT) design, with the treatment and the placebo being applied to the same hypothetical research population.

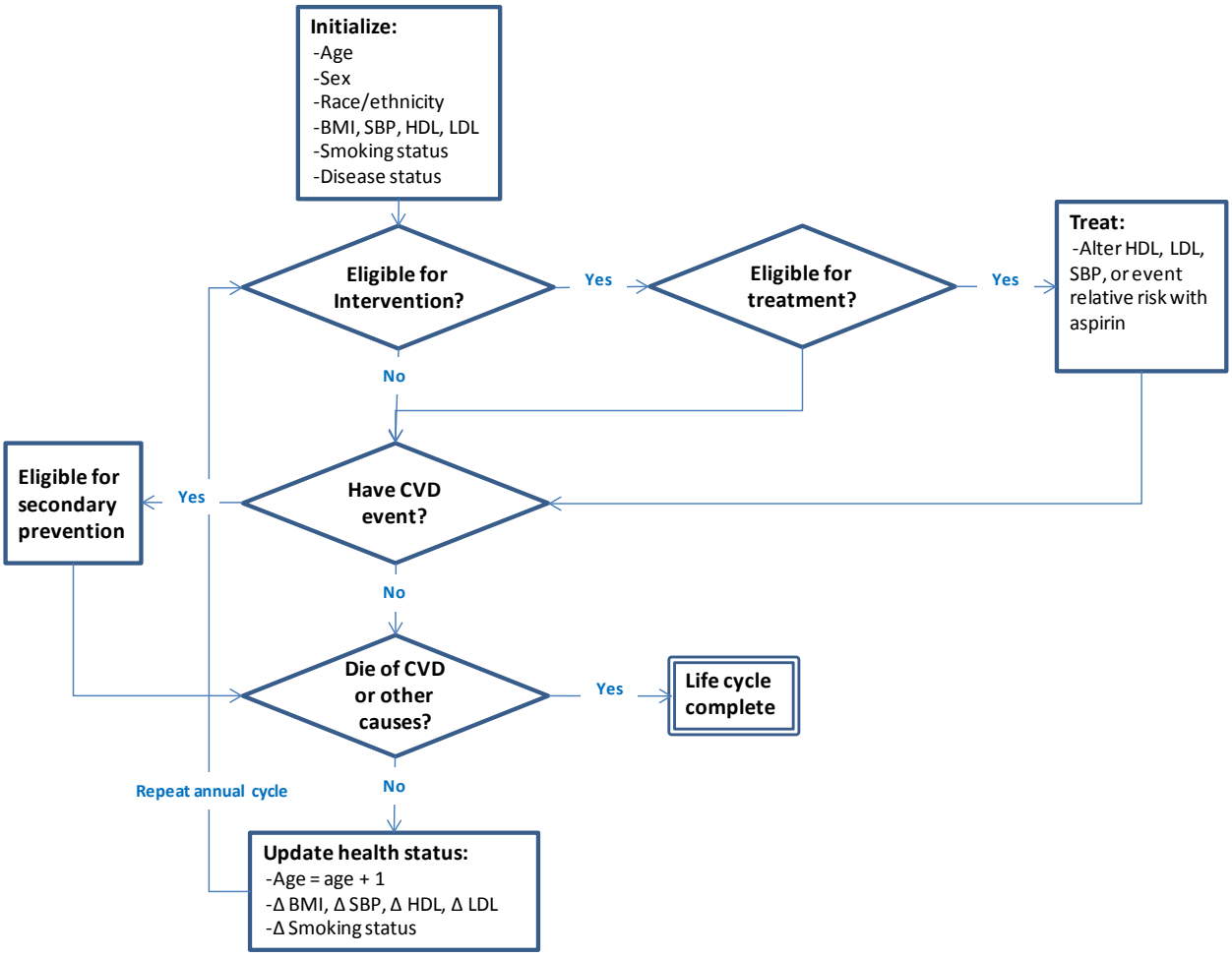
2 Model description

ModelHealth: CVD involves a considerable number of "moving parts." To provide a high-level overview before proceeding to model specifics, this section briefly describes the general mechanisms underlying the model design.

Initialization

Figure B1 illustrates the process flow of ModelHealth: CVD. As a microsimulation, the unit of observation is a hypothetical person. Each new simulation first involves initializing a person at a specific age (e.g., 40), with individual characteristics (such as sex and race/ethnicity) and initial health parameters (such as cholesterol and blood pressure levels and BMI) all drawn from U.S. statistically representative distributions. Thereafter, ModelHealth: CVD simulates the hypothetical person's lifespan and the natural history of cardiovascular disease using annual Markov cycles.

Appendix B Figure 1. ModelHealth: CVD Flow Diagram



Preventive Services

At the beginning of each annual Markov cycle, the model determines whether the simulated individual receives a preventive service, such as a screen for hypertension or high cholesterol or aspirin counseling. Eligibility for preventive services may be dictated by the parameters of a policy intervention—such as aspirin use among all persons older than age 40 without prior history of GI bleeding or hemorrhagic stroke in the treatment arm—or by contemporary rates of background preventive services (i.e., applied to both policy arms) observed in the population. Upon receiving a preventive service, the model determines whether the individual is eligible for treatment (e.g., taking statins for high cholesterol). Pharmacological treatment criteria for dyslipidemia and hypertension are implemented to be consistent with the Adult Treatment Panel III [3] and the JNC-7 [4] recommendations, respectively.

Treatment

The effect of treatment for high cholesterol or high blood pressure is realized through its impact on high- and low-density lipoprotein cholesterol (HDL-C/LDL-C) or systolic blood pressure (SBP), respectively. For example, an individual with high cholesterol could be treated with a statin and see a 30 percent reduction in LDL and a 10 percent increase in HDL, but taking a statin does not translate to a direct reduction in the

individual's risk of a myocardial infarction. Instead, these changes will translate to lowered risk of disease, as determined by the customized risk engine described in the following section. In contrast, taking aspirin on a daily basis directly alters the relative risk of having an event (such as a myocardial infarction or a gastrointestinal bleed).

Disease Events

The next step in each annual Markov cycle (following prevention/treatment) is to determine whether the individual experiences any non-fatal disease events during that year. Specifically, a person may: (1) have a myocardial infarction, (2) have an ischemic stroke, (3) have a hemorrhagic stroke, (4) experience angina pectoris, (5) develop congestive heart failure, (6) develop intermittent claudication, (7) develop diabetes, (8) experience a gastrointestinal bleed, (9) develop CRC, and/or (10) develop another type of cancer. The annual risks of (1)-(7) are determined by equations derived specifically for this model using data from the Framingham Heart Study [5, 6]. If a person has a cardiovascular event—that is, one or more of (1)-(6)—and survives, that person becomes eligible for secondary prevention. Treatment for dsylipidemia and hypertension for secondary prevention similarly based on ATP III and JNC-7 guidelines, respectively, and men and women who have a non-fatal myocardial infarction or ischemic stroke are also eligible for aspirin chemoprophylaxis.

Each year a person also faces a risk of dying from cardiovascular disease, a fatal case of cancer, or from other causes. The annual risk of death from CVD-related causes also is based on a study-specific equation derived from the Framingham Heart Study. The probability that a cancer episode is fatal is derived from Centers for Disease Control and Prevention (CDC) data. The probability of dying from a cause other than CVD or cancer is derived from U.S. life tables. A person who dies of any cause—or reaches the age of 100—exits the model, lifecycle complete.

Aging and Progression of Natural History

Finally, when a person survives a cycle, that individual's health status and parameters must be transitioned for the next cycle. Each cycle is annual, and therefore, the individual's age will simply increment by one. Cardiovascular risk factors—namely, HDL, LDL, SBP, and BMI—naturally progress over time, and annual transitions are modeled by a two-step process. First, it is determined whether the individual's risk factor increases, decreases, or stays the same. These probabilities are based on a multinomial logistic equation (which accounts for age, previous values, and other individual characteristics). Second, if a specific risk factor is determined to increase or decrease, a secondary set of equations determines the size of this change. The process repeats itself until the simulated person dies (or reaches age 100).

3 Model Data Sources and Parameters

A computational model with the degree of detail contained within ModelHealth: CVD requires a considerable amount of data and scientific evidence to specify all necessary parameters and inform the key transitional mechanisms. This lengthy section describes all the data sources (and in cases, assumptions) required for the model to operate.

3.1 Parameter Initialization

Each iteration of ModelHealth: CVD begins with the initialization of a new representative individual to simulate. Initial demographic characteristics, including age, sex, race/ethnicity, and U.S. Census region, are derived from the American Community Survey three-year sample [7]. Analyses for this study were stratified

by 10-year age group, sex, and baseline 10-year CVD risk. Persons meeting the characteristics of each strata are oversampled from the characteristics of the general U.S. population. Initial education is derived from the combined 2009-2012 Current Population Surveys [8]. Initial CVD risk factors, including BMI, SBP, LDL, and HDL are derived from the combined 2001-2010 National Health and Nutrition Examination Survey (NHANES) surveys [9-13]. Diabetes and prior CVD status at model initialization also are derived from the combined NHANES surveys. Initial smoking status is derived from the 2007 National Health Interview Survey[14] and calibrated to estimates by the Congressional Budget Office [15]. Initial smoking status is described in Section 3.6. Baseline characteristics of the simulated U.S. population cross-section are presented in **Table B1**.

Appendix B Table 1. Baseline Characteristics of Simulated U.S. Population Cross-Section (Ages 35+)

	All (N=162.8 million)	Source
Age		NHANES (2001-2010) [9-13]
35-44	25.3%	ACS 3yr (2011) [7]
45-54	27.5%	ACS 3yr (2011) [7]
55-64	22.6%	ACS 3yr (2011) [7]
65-74	13.4%	ACS 3yr (2011) [7]
75+	11.2%	ACS 3yr (2011) [7]
% female	52.4%	ACS 3yr (2011) [7]
Education		
High school or less	44.3%	CPS (2009-2012) [8]
Some college	25.6%	CPS (2009-2012) [8]
4-year degree or more	30.0%	CPS (2009-2012) [8]
BMI (mean, kg/m^2)	29.0	NHANES (2001-2010) [9-13]
% overweight	72.4%	NHANES (2001-2010) [9-13]
% obese	40.9%	NHANES (2001-2010) [9-13]
SBP (mean, mm Hg)	126.1	NHANES (2001-2010) [9-13]
% over goal	20.6%	NHANES (2001-2010) [9-13]
% treated	22.0%	NHANES (2001-2010) [9-13]
LDL (mean, mg/dL)	120.3	NHANES (2001-2010) [9-13]
% over goal	28.3%	NHANES (2001-2010) [9-13]
% treated	22.5%	NHANES (2001-2010) [9-13]
% smokers	17.4%	NHIS (2008) [14], CBO(2012) [15]
% with diabetes	18.7%	NHANES (2001-2010) [9-13]
% with previous CVD	12.8%	NHANES (2001-2010) [9-13]

Notes: SBP = systolic blood pressure; SSI = Supplemental Security Income; BMI = body mass index; LDL = low-density lipoprotein; CVD = cardiovascular disease; NHANES = National Health and Nutrition Examination Survey; ACS = American Community Survey; CPS = Current Population Survey; NHIS = National Health Interview Survey; CBO = Congressional Budget Office.

3.2 Progression of Risk Factors

After each annual Markov cycle in ModelHealth: CVD, an individual's time-dependent attributes must be transitioned to reflect the age progression and natural history of cardiovascular disease risk factors over one's lifetime. A person's age simply increments by one, but the remaining risk factors (BMI, HDL, LDL, and SBP) transition according to a two-step process. Change in smoking status is described in Section 3.6.

Step 1: Determine probability that a risk factor changes

In the first step of the process, a person faces a probability of increasing, decreasing, or staying the same in a particular risk factor. For LDL, HDL, and BMI, staying the same is defined as a change of +/-1 percent per year. Due to the greater variability in measuring blood pressure, staying the same in SBP is classified as being within +/-3.5 percent per year. In all cases, these probabilities were estimated using multinomial logistic regression. HDL, LDL, and SBP were estimated using annualized Framingham Heart Study data adjusting for age, sex, and BMI [5, 6]. BMI was estimated from Behavioral Risk Factor Surveillance System (BRFSS) survey data (from current weight and previous year recall) adjusting for age, sex, and race/ethnicity [16].

For year-to-year BMI transitions, the increasing or decreasing cases were split in two additional sub-cases. Specifically, one allows for small changes or "drifting" (i.e., an increase or decrease of 1 to 5 percent), and the other accommodates larger changes (i.e., an increase or decrease of 5 percent or more). Our analysis of Framingham Heart Study and BRFSS data indicate that these weight-change modalities reflect what people typically experience in real life, and the probabilities of each modality shift as we age. For example, a typical male may be most at risk for significant weight gain in his 20s, be more likely to have his BMI drift up in his 30s and 40s, and then face a stronger tendency towards weight stabilization in his 50s and 60s.

Step 2: Determine size of risk factor change

Once a person's transition modality has been determined, the second step is to determine the size of the change. Age, sex, and (in the case of BMI) race/ethnicity-specific equations were estimated for each of these cases. Whereas the first step in the process is stochastically determined in each cycle (i.e., facing a probability of each scenario), the second step is deterministic, with the transition applied as a percentage change (or zero change, in the case that a risk factor remains stable from the previous year). **Table B2** summarizes the details of this two-step process of year-on-year transitions of risk factors.

Appendix B Table 2. ModelHealth: CVD Annual Progression of Risk Factors

Step	Case	Source	Controlled Factors	Estimator
1	P(BMI Change)	BRFSS [16]	Age, sex, race/ethnicity, previous BMI	Multinominal Logit
1	P(HDL Change)	Framingham [5, 6]	Age, sex, BMI, previous HDL	Multinominal Logit
1	P(LDL Change)*	Framingham [5, 6]	Age, sex, BMI, previous LDL	Multinominal Logit
1	P(SBP Change)	Framingham [5, 6]	Age, sex, BMI, previous SBP	Multinominal Logit
2	Q(BMI Change)	BRFSS [16]	Age, sex, race/ethnicity, previous BMI	OLS
2	Q(HDL Change)	Framingham [5, 6]	Age, sex, BMI, previous HDL	Random Effects
2	Q(LDL Change)*	Framingham [5, 6]	Age, sex, BMI, previous LDL	Random Effects
2	Q(SBP Change)	Framingham [5, 6]	Age, sex, BMI, previous SBP	Random Effects

Notes: P() = probability. Q() = quantity. OLS = Ordinary least squares regression. BRFSS = Behavioral Risk Factor Surveillance System. *In actuality, the progression of LDL is more complex than indicated in the table and text. LDL was not measured with the same regularity as HDL and total cholesterol in the Framingham Heart Study; therefore, transitions in LDL were modeled in additional two steps. First, the probability and quantity of change in total cholesterol was modeled as described above. Second, HDL and total cholesterol were used in a prediction equation—derived from NHANES with high explanatory power (i.e., $R^2 > 0.9$)—to estimate a corresponding LDL level. Although not included in the prediction equations, estimations related to changes in cholesterol and blood pressure controlled for treatment.

3.3 Risk of Cardiovascular Disease Events

Published risk calculators for cardiovascular disease—such as PROCAM [17], SCORE [18], QRisk [19], or those derived from the Framingham Heart Study[20]—generally estimate an individual's 10-year risk of disease. These are difficult to translate to a Markov model with annual cycles. In addition, existing risk profiles commonly combine outcomes (such as chronic heart disease or cardiovascular disease, generally, compared to myocardial infarction or ischemic stroke, specifically—for example, see [21]). The distinction is particularly important to accurately estimating costs associated with disease. They may also exclude potentially policy-relevant risk factors (such as differentiating current smokers from recent quitters or former smokers), and/or include clinical risk factors that may not be salient to population-level policy evaluation (such as evidence of left ventricular hypertrophy in the risk of stroke—for example, see [22]). For these reasons, we used data from the Framingham Heart Study to derive and develop customized 1-year risk equations for use in ModelHealth: CVD.

We developed risk equations for eight outcomes: myocardial infarction (MI), ischemic stroke, hemorrhagic stroke, angina pectoris, congestive heart failure, intermittent claudication, non-specific cardiovascular disease-related death, and diabetes. The risk analysis uses the Original Cohort (beginning in 1948 with 5,209

attendees) and the Offspring (beginning in 1971 with 5,124 attendees) arms of the Framingham Heart Study. Data were sourced from the National Heart, Lung, and Blood Institute's (NHLBI's) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), with approval and human subjects oversight from the HealthPartners Institute for Education and Research's Institutional Review Board [5, 6]. Statistical survival analysis was performed using Stata, Version 11 (Statacorp, College Station, TX).

To use as much of this rich data source as possible, allow for time-varying covariates, and provide for a direct estimate of annual risk, we adopted a parametric over the more common semi-parametric Cox proportional hazard approach in our analysis. Similar parametric methods have been previously explored and validated by Framingham Heart Study researchers [23]. Age, BMI, HDL, LDL, SBP, and one's disease history are all included as potential time-varying covariates in the analyses.

Because age accounts for time within a single person's life and because we do not have strong evidence with respect to the impact of secular time trends, we estimated an individual's risk using the exponential proportional hazards model (which has a time independent or "memoryless" property). Specifically, estimation was conducted using the *streg* command in Stata. Time independence is particularly important when estimating annual risk (i.e., t = 1), because the additional information in the shape parameter (i.e., embodied in the so-called accelerated failure time metric) is never appropriately used and may otherwise systematically over-or under-estimate risk in a one year context. The resulting exponential model is estimated with a person j likelihood function of the risk of an event $\left(d_j \in \{0,1\}\right)$ between t_{0j} and t_j is

$$L_j = \left[\frac{e^{\left(-e^{\beta_0 + x_j\beta}\right)t_j}}{e^{\left(-e^{\beta_0 + x_j\beta}\right)t_{0j}}}\right]\left(e^{-e^{\beta_0 + x_j\beta}}\right)^{d_j}$$

with an individual's probability of an event in the next year equal to $F(1) = 1 - e^{\left(-e^{\beta_0 + x_j\beta}\right)}$.

Appendix B Table 3. Summary of Risk Equations Derived From Framingham Heart Study Data

Risk of Non-fatal Myocardial Infarction (MI)

	Hazard Ratio	Z-Score
Age	1.039	14.09
Sex	0.380	-13.77
HDL	0.986	-5.31
LDL	1.005	8.08
SBP	1.013	9.60
Smoke	1.698	8.00
Diabetes	1.889	7.38
Previous CVD	2.784	14.33

Risk of Angina Pectoris (AP)

	Hazard Ratio	Z-Score
Age	1.024	9.88
Sex	0.587	-8.42
HDL	0.989	-4.62
LDL	1.006	11.95
SBP	1.011	8.90
Previous CVD	2.750	13.84

Risk of Non-fatal Ischemic Stroke (IS)

	Hazard Ratio	Z-Score
Age	1.067	16.76
HDL	0.988	-3.92
SBP	1.023	14.31
Smoke	1.627	5.02
Diabetes	1.913	6.02
Previous CVD	2.005	7.60

Risk of First Congestive Heart Failure (CHF)

	Hazard Ratio	Z-Score
Age	1.074	22.35
HDL	0.986	-5.49
SBP	1.015	10.65
BMI	1.024	3.43
Smoke	1.401	4.15
Diabetes	2.176	9.92
Previous MI	3.885	17.76
Previous Other CVD	1.838	8.22

Risk of First Hemorrhagic Stroke (HS)

	Hazard Ratio	Z-Score
Age	1.049	6.64
SBP	1.020	5.94
BMI	0.904	-4.75
Smoke	1.497	2.15
Previous CVD	1.568	2.35

Risk of Diabetes

	Hazard Ratio	Z-Score
Age	1.064	30.67
BMI	1.108	20.90
SBP	1.004	2.91
HDL	0.968	-13.72

Risk of Intermittent Claudication (IC)

	Hazard Ratio	Z-Score
Age	1.039	10.39
Sex	0.619	-5.32
HDL	0.993	-2.01
LDL	1.007	8.35
SBP	1.015	8.65
Smoke	2.871	12.05
Diabetes	2.237	7.20
Previous CVD	2.529	9.93

Risk of CVD-related Death

	Hazard Ratio	Z-Score
Age	1.069	27.43
Sex	0.495	-13.01
LDL	1.004	6.79
SBP	1.009	9.15
Smoke	1.589	7.97
Diabetes	1.590	7.21
Previous MI	1.455	5.80
Previous IS	1.759	7.37
Previous HS	57.313	28.06
Previous CHF	9.270	35.46
Previous Other CVD	1.930	11.31

Source: Author's analysis of data from the Framingham Heart Study [5, 6]. Notes: Estimations are based on the exponential proportional hazards model. All continuous variables used in ModelHealth: CVD are natural log transformed; however, hazard ratios of non-log variables are presented here instead for easier interpretations.

Baseline Risk of GI Bleeding Events

We estimate the baseline risk of gastrointestinal (GI) bleeding events using an analysis of Italian observational data [24]. Generally speaking, evidence suggests that men face higher risk of GI bleeds than women, and risk for both sexes increases with age. Probabilities for GI bleeding events are summarized in **Table B4** below.

Appendix B Table 4. Summary of Risk for GI Bleeding Events in ModelHealth: CVD

	Age 40-49	Age 50-59	Age 60-69	70-79	Age 80+
Men	0.5%	1.2%	2.1%	3.9%	6.1%
Women	0.3%	0.7%	1.3%	2.3%	3.6%

Source: [24]. Note: Values represent estimated major GI bleeds are adjusted for the age and sex distribution of the US population.

3.4 Treatment Effects

Aspirin for Primary Prevention

Model parameters for primary prevention are summarized in **Table B5**. CVD and bleeding relative risks were derived from seven low-dose primary prevention trials, defined as 100mg of aspirin per day or less, identified by the systematic evidence review [25-32].

Appendix B Table 5. Summary of Aspirin Treatment Effects (RR) for Primary Prevention of Cardiovascular Disease

Condition	Prevention Type	Sex	Low	Base Case	High
Relative Risk of Myocardial Infarction	Primary	Men	0.97	0.85	0.75
Relative Risk of Ischemic Stroke	Primary	Men	0.95	0.82	0.71
Relative Risk of Hemorrhagic Stroke	Primary	Men	1.00	1.14	1.57
Relative Risk of CVD-related Death	Primary	Men	1.00	1.00	0.84
Relative Risk of GI Bleed	Primary	Men	1.29	1.59	1.97
Relative Risk of CRC incidence	Primary	Women	0.77	0.60	0.47

Sources: [25-32].

Aspirin for Secondary Prevention

Aspirin also may be initiated following a non-fatal CVD event for the purposes of reducing the risk of subsequent events (secondary prevention). A recent meta-analysis of 16 secondary prevention aspirin trials indicates a 31 percent reduction in MI risk (95% Rate Ratio [RR] CI: 0.60-0.80) and a 22 percent reduction in ischemic stroke risk (95% RR CI: 0.61-0.99) [33]. Similar to the primary prevention trials, secondary preventive use of aspirin does not show a statistically significant reduction in CVD-related or all-cause mortality.

Due to the relative rarity of hemorrhagic stroke and major GI bleeding and the smaller sample sizes of participants in secondary trials, the estimates of increased risk of adverse events from aspirin in secondary prevention are less precise. Instead of using these less precise estimates, we assume the increased risk of hemorrhagic stroke and GI bleeding from aspirin use in secondary prevention is the same as observed in the primary prevention trials. In all cases, we draw an individual-specific effect size from a triangle distribution based on the 95 percent confidence intervals. A summary of the aspirin treatment effects when used for primary prevention of CVD is given in **Table B6**.

Appendix B Table 6. Summary of Aspirin Treatment Effects for Secondary Prevention of Cardiovascular Disease

Condition	Prevention Type	Sex	Low	Mid	High
Relative Risk of Myocardial Infarction	Secondary	Men	0.8	0.69	0.6
Relative Risk of Myocardial Infarction	Secondary	Women	0.8	0.69	0.6
Relative Risk of Ischemic Stroke	Secondary	Men	0.99	0.78	0.61
Relative Risk of Ischemic Stroke	Secondary	Women	0.99	0.78	0.61
Relative Risk of Hemorrhagic Stroke	Secondary	Men	1.05	1.42	1.93
Relative Risk of Hemorrhagic Stroke	Secondary	Women	1.05	1.42	1.93
Relative Risk of CVD-related Death	Secondary	Men	1	1	1
Relative Risk of CVD-related Death	Secondary	Women	1	1	1
Relative Risk of GI Bleed	Secondary	Men	1.38	1.63	1.93
Relative Risk of GI Bleed	Secondary	Women	1.38	1.63	1.93

Sources: [33].

Statins

Due to the overwhelming use of statins (i.e., HMG-CoA reductase inhibitors) in the treatment of high cholesterol—recent estimates suggest rates in excess of 90 percent of Americans seeking pharmacological treatment [34]—we simplified treatment of dyslipidemia in ModelHealth: CVD to this drug class. We used several recent (and/or otherwise relevant) meta-analyses/reviews of statins to identify major (of 1,000 or more persons) randomized controlled trials comparing lipid reduction associated with statins to a placebo [35-40]. Included trials—accounting for a total of 67,815 subjects—had a follow-up period of at least 52 weeks, involved subjects for primary or secondary prevention, were subject-blinded (at a minimum), and reported changes in LDL or HDL cholesterol as an outcome. Trials were excluded if additional (open label) lipid-lowering drugs were allowed for use in the placebo group (unless observed at rates lower than 10 percent). The trials included in our analysis are summarized in **Table B7**.

Appendix B Table 7. Summary of Statin Trials Included in Estimation of Treatment Effects

Trial	Subjects	Ages	Baseline LDL	Baseline HDL	Mean ↓LDL	Mean ↑ HDL
4S	4,444	30 – 70	188.3	45.8	47.1	3.7
AFCAPS/TEXCAPS	6,605	45 – 73	150.4	36.3	41.8	1.9
ALERT	2,102	30 – 75	158.5	52.2	36.7	0
ASCOT-LLA	10,305	40 – 79	133	50.7	46.4	0.8
ASPEN	2,410	40 – 75	113.5	47	33.1	0.9
HPS	20,536	40 – 80	131.5	42.5	50.3	0.8
LIPID	9,014	31 – 75	150	36	37.5	1.8
PROSPER	5,804	70 – 82	146.9	50.3	39.7	2.5
WOSCOPS	6,595	45 – 64	192	44	49.9	2.2

Sources: 4S [41]; AFCAPS/TEXCAPS [42]; ALERT [43]; ASCOT-LLA [44]; ASPEN [45]; HPS [46];[47]; PROSPER [48]; WOSCOPS [49].

To accommodate differential drug response according to baseline (only one included trial included stepped treatment in its experimental protocol [41]), we estimated treatment effects on cholesterol levels using a simple weighted ordinary least squares regression, with baseline LDL or HDL levels (respectively) as the only predictor:

$$Effect_{Chol} = \beta_0 + (BaselineChol)\beta_{BaselineChol}$$

The average effect size of statins on LDL was estimated to be a 42.9 mg/dL reduction, with an additional marginal impact of 0.014 mg/dL reduction per mg/dL of baseline LDL. The average effect size of statins on HDL was estimated to be a 2.2 mg/dL increase, with a marginal decremental impact of 0.017 mg/dL

reduction per mg/dL of baseline HDL. These results indicate that the typical lipid modifying response to statin therapy is not highly sensitive to baseline lipid levels.

To accommodate interpersonal differences in the impact of drug therapy on LDL cholesterol in ModelHealth: CVD, we constructed a triangle distribution centered on the mean effect size described above, with upper and lower limits defined by the standard deviation in effect size observed in statin trials, to draw person-specific effect sizes. We estimated the standard deviation in LDL cholesterol reduction using a meta-analysis of (generally smaller/shorter) placebo controlled trials rather than the major trials summarized in **Table B7**, because the primary endpoints in these trials were cardiovascular disease outcomes (and as a result, standard deviations in cholesterol changes were not typically reported). We did find not good evidence on the interpersonal variability of treatment effects from statins on HDL, and we incorporate only mean treatment effects in this case.

Finally, all trials—with exception of WOSCOPS [49]—reported results solely based upon intention-to-treat analyses. The average weighted adherence to the treatment across study arms among included trials reporting this measure was 89.4 percent. To account for diminished average treatment effects attributable to non-adherence to prescribed therapy, we estimate an appropriate adjustment by dividing lipid impact by 0.9 in the base case. Statin treatment effects in ModelHealth: CVD are summarized in **Table B8**.

Appendix B Table 8. Summary of Statin Treatment Effects

	β0	β*BaselineChol*	Standard Deviation	Adherence Adjustment
Statin Effect on LDL	42.881	0.014	24.382	0.90
Statin Effect on HDL	2.176	-0.017	N/A	0.90

Source: Analysis of clinical trials described in **Table B7**.

Antihypertensives

We used recent meta-analyses/reviews of antihypertensive therapy to identify major (of 1,000 or more persons) randomized controlled trials comparing blood pressure reduction associated with drug therapy to a placebo [50-58]. Included trials—accounting for a total of 54,863 subjects—had a follow-up period of at least 52 weeks, involved subjects for primary or secondary prevention, were subject-blinded (at a minimum), and reported changes in SBP as an outcome. In addition, due to the considerable heterogeneity in observed blood pressure lowering drug therapy strategies—including differences in first-line drugs, doses, and combinations [59]—we required treatment arm protocol to include stepped therapy (and preferably matched stepped therapy of a placebo in the control arm). Trials were excluded if additional (open label) blood pressure lowering drugs were allowed for use in the placebo group (unless observed at rates lower than 10 percent). The trials included in our analysis are summarized in **Table B9**.

Appendix B Table 9. Summary of Antihypertensive Drug Trials Included in Estimation of Treatment Effects

Trial	Subjects	Ages	Baseline SBP	Mean ↓ SBP
FEVER	9,711	50 – 79	154.3	4.5
HYVET	3,845	80+	173.0	13.0
MRC-1	17,354	35 – 64	161.5	10.5
MRC-2	4,396	65 – 74	173.0	15.5
PROGRESS	6,105	30 – 90	147.0	9.0
SHEP	4,736	60+	170.3	14.0
STOP	1,627	70 – 84	195.0	22.0
Syst-China	2,394	60+	170.5	9.1
Syst-Eur	4,695	60+	174.0	13.0

Sources: FEVER [60]; HYVET [61]; MRC-1[62], MRC-2[63]; PROGRESS[64]; SHEP[65]; STOP [66]; Syst-China[67]; Sys-Eur [68].

To accommodate diverse treatment strategies (i.e., stepped and combination) with respect to baseline blood pressure relative to goal, we estimated treatment effects on blood pressure levels using a simple weighted ordinary least squares regression, with baseline SBP levels (respectively) as the only predictor:

$$Effect_{SBP} = \beta_0 + (BaselineSBP)\beta_{BaselineSBP}$$

The average effect size of antihypertensive drugs on SBP was estimated to be a 40.1 mmHg increase, counterintuitively, but this is offset by an additional marginal impact of 0.31 mmHg reduction per mmHg of baseline SBP (**Table B10**). Hence, the intercept on the treatment effect is negative, implying that antihypertensives begin to raise blood pressure around SBP baseline levels of 108 mmHg or lower. In practice, this threshold is well below standard SBP goals (140 mmHg for most patients, 135 mmHg for diabetics), and such blood pressure raising effects will not be invoked by the model.

To accommodate interpersonal differences in the impact of drug therapy on SBP in ModelHealth: CVD, we constructed a triangle distribution centered on the mean effect size described above, with upper and lower limits defined by the standard deviation in effect size observed in the antihypertensive trials, to draw person-specific effect sizes. The standard deviation of drug treatment on SBP was estimated from the subset of trials from **Table B9** that reported this measure [61, 67, 68].

Finally, all trials reported results solely based upon intention-to-treat analyses. The average weighted adherence to the treatment across study arms among included trials reporting this measure was 81.9 percent. To account for diminished average treatment effects attributable to non-adherence to prescribed therapy, we estimate an appropriate adjustment by dividing lipid impact by 0.8 in the base case. Average blood pressure lowering effects of antihypertensive drugs used in ModelHealth: CVD are summarized in **Table B10**.

Appendix B Table 10. Summary of Antihypertensive Drug Treatment Effects

	$\beta 0$	$\beta BaselineSBP$	Standard Deviation	Adherence Adjustment
Antihypertensive Drug Effect on SBP	-40.101	0.310	16.90	0.80

Source: Analysis of clinical trials described in **Table B9**.

3.5 Acceptance of Screening and Adherence to Treatment

Good evidence is lacking for the percentage of individuals who would accept prevention screening/counseling—in accordance with USPSTF recommendations—when offered. We assume 90 percent of individuals will accept any of the USPSTF-recommended clinical preventive services. This is implemented as a person-level parameter, such that a person who accepts screening will always do so and one who does not accept, will never do so.

Good and consistent evidence is also lacking for long-term adherence rates among those taking aspirin or drug therapy for the prevention of cardiovascular disease. Treatment adherence rates from clinical trials are generally not representative of the population. Individuals who enroll in a clinical trial are believed to be more motivated to regularly take study drugs, and clinical trial subjects also tend to receive more consistent and intensive attention from healthcare providers than does the general population. Retrospective or claims-based studies capture a more representative population (although, generally biased toward over-representing those with health insurance coverage), but these studies are likely to miss patients who are prescribed treatment but never fill a prescription (i.e., primary non-adherence) and overstate nonadherence for patients lost to other insurers, providers, lost coverage, etc. Due to such limitations, we restrict our assumptions to point estimates of average adherence in the cases of primary and secondary prevention.

Evidence regarding differences in adherence to lipid modifying and blood pressure lowering drug ther-

apies is mixed [69-72]. Although factors such as cost (statin therapy is generally more expensive than antihypertensive therapy) and regimen complexity (antihypertensive treatment strategies can often incorporate use of two, three, or even four drugs in combination) could drive differences in adherence in drug therapies, we simplify by assuming similar average adherence between treating lipids and hypertension. Systematic reviews of antihypertensives show long-term adherence (i.e., 2 years or more) ranging typically (varying considerably by drug class) from 30 to 50 percent, with shorter-term adherence (i.e., 1 year or less) a bit higher [73, 74]. A recent review of adherence to statins shows slightly wider estimates in long-term adherence, typically ranging from roughly 20 to 70 percent [75]. Analyses in both cases suggest prior cardiovascular disease increases likelihood as much as 50-70 percent [75-77]. Taking this all into account, we assume 40 percent adherence to statins and antihypertensives for primary prevention in the base case, and we assume 60 percent adherence for secondary prevention.

Appendix B Table 11. Summary of Treatment Adherence Assumptions in ModelHealth: CVD

Treatment	Prevention Type	Adherence (Base Case)	Sensitivity Range
Aspirin	Primary	50%	20 – 70%
Aspirin	Secondary	70%	50 – 90%
Statins	Primary	40%	20 – 60%
Statins	Secondary	60%	40 – 80%
Antihypertensives	Primary	40%	20 – 60%
Antihypertensives	Secondary	60%	40 – 80%

Source: Author's assumptions based on evidence reported in the literature [69-78].

3.6 Modeling smoking behavior

Overview

Individuals may be in one of four smoking states: never smoker, current smoker, recent quitter, or former smoker. The probability that an individual is in a given smoking state is determined by two sets of multivariate risk equations that account for age, sex, race/ethnicity, and—for those older than age 25—the lifetime educational attainment at introduction into the model. Similarly, the likelihood that an agent who is currently in the never-smoker state begins smoking within a given cycle is conditioned on his/her age, sex, race/ethnicity, and—if older than age 25—lifetime educational attainment. Two different data sources informed these risk equations. Estimates of risk equations corresponding to ages 18 and younger used Youth Risk Behavior Survey (YRBS) data [79]. Estimates of risk equations corresponding to ages 19 and older used data from the National Health Interview Survey (NHIS) [14].

Although the specific final multivariable risk equations vary in terms of covariates and dependent variables, several criteria were consistent. The statistical relationships between each covariate and other predictors were screened. If inclusion of a covariate violated assumptions (e.g., co-linearity, normality, disproportionate cell size) appropriate adjustments (e.g., center around mean, transformation, re-categorization) were made or its inclusion reconsidered. Interaction terms (e.g., differential rates of initiation between young women and young men, differential rates of cessation between African-Americans with higher education and those without a high-school diploma, etc.) were considered based on the following criteria: representing at least 10% of the larger groups (e.g., at least 10% of women and at least 10% of those younger than age 18, at least 10% of African-Americans within each educational category, etc.), and a coefficient significant at the 10% level.

Initial smoking status

A multinomial logistic regression with outcomes corresponding to the four smoking states was used to estimate the likelihood of an individual having an initial smoking status given his/her age, sex, race/ethnicity, and lifetime educational attainment. The estimated distribution across potential smoking states was used to determine each agent's initial smoking status at introduction into the model.

Neither the YRBS nor the NHIS directly asks respondents about their current smoking status. Instead, the following definitions were used:

Never smoker: Having smoked fewer than 100 cigarettes in their lifetime

Current smoker: Having smoked at least 100 cigarettes in their lifetime and having smoked in the last week

Recent quitter: Having smoked at least 100 cigarettes in their lifetime and having quit for less than 4 years

Former smoker: Having smoked at least 100 cigarettes in their lifetime and having quit for 4 or more years

The usual definitional prerequisite of having smoked at least 100 cigarettes in their lifetime was applied to exclude experimental smoking. The results of the estimation are contained in **Table B12**. Time in state (i.e., the number of years as a smoker and/or the number of years since quitting) partially determines the likelihood of quitting or relapsing. An age of initiation is assigned to those initialized as current smokers, recent quitters, or former smokers. For those initialized as recent quitters or former smokers, an age of cessation also is assigned.

Smoking status initialization is implemented in a two-step process. In Step 1, for all agents initialized as a current smoker, recent quitter, or former smoker, a random draw (from a distribution drawn configured to initiation rates estimated from the NHIS) determines the age at which the person first started smoking (e.g., age 19). Then, for those initialized as recent quitters and former smokers (Step 2), a random draw from a second distribution configured to cessation rates estimated from NHIS and truncated at the age of initiation determines the age of cessation (e.g., age 26). These two ages are used to determine the time spent smoking and time since cessation, which are used in the model when determining future smoking behavior.

Appendix B Table 12. Results of Multinomial Estimation Predicting Initial Smoking Status

	Current Smoker	*95% Conf Interval*	Former Smoker	*95% Conf Interval*
Ref. Category	-0.798	*(-0.874 , -0.722)*	-1.922	*(-2.029 , -1.816)*
Female	-0.453	*(-0.495 , -0.411)*	-0.605	*(-0.646 , -0.564)*
24-44	0.559	*(0.482 , 0.635)*	1.151	*(1.039 , 1.263)*
45-64	0.541	*(0.462 , 0.621)*	1.813	*(1.702 , 1.925)*
65+	-0.538	*(-0.632 , -0.443)*	2.203	*(2.090 , 2.315)*
Black	-0.475	*(-0.535 , -0.416)*	-0.714	*(-0.779 , -0.648)*
Hispanic	-1.249	*(-1.322 , -1.176)*	-0.723	*(-0.788 , -0.659)*
Other	-0.702	*(-0.799 , -0.604)*	-0.793	*(-0.893 , -0.694)*
High School	0.688	*(0.634 , 0.741)*	0.112	*(0.054 , 0.169)*
Post-Secondary	-1.293	*(-1.356 , -1.230)*	-0.394	*(-0.442 , -0.346)*

Source: NHIS [14].

Lifetime smoking behavior

An individual's "risk" of changing smoking status (i.e., transitioning to another smoking state), is determined by current state, time in that state, and demographics. Individuals who have never smoked can either remain in the never smoker state or begin smoking and transition to the current smoker state. A current smoker who is in the current smoker state can remain or quit and transition to the recent quitter state. A recent quitter either remains in the recent quitter state, relapses into the current smoker state, or moves to the former

smoker state once four years have passed. A former smoker either relapses into the current smoker state or remains in the former smoker state.

Three separate logistic regressions determine the risk of smoking initiation by comparing initiators to never smokers. The first, which uses YBRS data, applies to ages younger than 18. The second and third, which use NHIS data, applied to ages 18-24 and 25 and older, respectively. Similar to the initial smoking status risk equations, the 19-24 specification was distinguished by inclusion of lifetime educational achievement. **Tables B13** and **B14** contain the results of these estimations.

We assumed no cessation among youth younger than age 18 and estimated two cessation risk equations for adults. From the NHIS data, we identified quitters as those indicating they had ceased cigarette use within the last 12 months with no indication of relapse. Two logistic regressions (18-24 and 25 and older) compared quitters to current smokers to determine the likelihood of smoking cessation. Once again, the 19-24 specification was distinguished by inclusion of lifetime educational achievement.

Relapse after quitting tobacco use is time-sensitive. The longer a person has successfully quit smoking, the less likely he or she is to relapse. The cross-sectional design of both the YBRS and NHIS surveys made estimation of relapse rates that account for time since cessation difficult. Instead, we used published estimates based on longitudinal studies. These values were adjusted during calibration to provide reasonable values of age-, sex-, and race/ethnicity-specific tobacco use rates. **Table B15** contains these rates.

Appendix B Table 13. Youth Tobacco Smoking Initiation Rates

Age	Male	Female
8	0.002	0.006
9-10	0.005	0.006
11-12	0.010	0.013
13-14	0.022	0.021
15-16	0.027	0.027
17-18	0.010	0.013

Source: YBRS [79].

Appendix B Table 14. Results of Logistic Regressions Predicting Adult Smoking Status

	Tobacco Initiation	*95% Con Interval*	**Tobacco Cessation**	*95% Conf Interval*
Ref. Category	-27.7099	*(-33.273 , -22.146)*	-1.772	*(-2.133 , -1.411)*
Female	3.5358	*(4.351 , 2.721)*	-0.046	*(-0.053 , -0.039)*
24-44	9.814	*(12.472 , 7.156)*	-0.1545	*(-0.179 , -0.130)*
xFemale	-10.0481	*(-12.656 , -7.440)*	-0.00165	*(-0.002 , -0.001)*
45-64	10.441	*(12.846 , 8.036)*	-0.1181	*(-0.139 , -0.098)*
xFemale	-5.817	*(-7.292 , -4.342)*	0.2346	*(0.294 , 0.175)*
White	-6.3501	*(-7.745 , -4.955)*	0.2966	*(0.369 , 0.224)*
xFemale	-3.8882	*(-4.893 , -2.884)*	Not Significant	
Black	3.4254	*(4.151 , 2.700)*	-0.0603	*(-0.073 , -0.048)*
xFemale	-3.4627	*(-4.426 , -2.499)*	Not Significant	
Hispanic	5.0037	*(6.435 , 3.572)*	0.0776	*(0.094 , 0.062)*
xFemale	-0.0798	*(-0.096 , -0.063)*	Not Significant	
No High School	6.5959	*(8.319 , 4.872)*	-0.00755	*(-0.009 , -0.006)*
xFemale	-3.8882	*(-4.791 , -2.986)*	Not Significant	
High School	9.2186	*(11.708 , 6.729)*	0.0191	*(0.022 , 0.016)*
xFemale	-3.4627	*(-4.365 , -2.561)*	Not Significant	
Post-Secondary	4.5348	*(5.593 , 3.477)*	0.3067	*(0.384 , 0.230)*
xFemale	-0.0798	*(-0.096 , -0.064)*	Not Significant	

Source: NHIS [14]. Note: Reference category is young, mixed-race, male.

Appendix B Table 15. Baseline Smoking Tobacco Relapse Rates

Years Since Successful Quit	Probability of Relapse	Source
1	0.37	Hughes 2003 [80]
2	0.08	Wetter (2004) [81]
3	0.08	Wetter (2004) [81]
4	0.08	Wetter (2004) [81]
5	0.08	Wetter (2004) [81]
6	0.038	Wetter (2004) [81]
7	0.038	Wetter (2004) [81]
8	0.021	Wetter (2004) [81]
9	0.021	Wetter (2004) [81]
10	0.021	Wetter (2004) [81]
11	0.005	Wetter (2004) [81]

Calibration of smoking behaviors to CBO model

Tobacco prevalence was calibrated to reflect baseline tobacco use projections of the Congressional Budget Office (CBO) prior to final analysis [15]. These calibrated initiation and cessation rates are used for all estimates. We were unable to obtain details regarding how the CBO parameterizes specific population groups. Instead, we worked with estimates derived from Figure 1-1 in the 2012 CBO report (page 3) [15]. CBO only reports its projection of smoking prevalence among all adults in Figure 1-1. Our model determines annual smoking prevalence based on initiation, cessation and relapse, as mediated by sex, age, race-ethnicity and educational attainment. The average adult smoking prevalence reported in Figure 1-1 of the CBO report could have been be reproduced with infinite number of changes to patterns of smoking initiation, cessation, and relapse rates among males and females of different ages, race/ethnicities, and educational attainment. In addition, predictions of smoking prevalence among adults depend heavily on recent, current and near-term teen smoking initiation rates. Therefore, with only Figure 1-1 and a general description of the CBO's approach as a guide, we tested a reasonable set of parameter modifications to adjust the smoking prevalence rates produced by our model over the next 10 years to better reflect CBO's baseline.

Three key sources of deviation from the CBO model were identified and adjusted for within the model. The first source was the estimated initiation patterns from NHIS age-based categories that created a stepped function and subsequent "jagged" initiation patterns. The resolution was to smooth initiation rates using a moving average process across ages that held constant prevalence within each age group. This adjustment removed "jumps" in prevalence among birth cohorts, but initiation remained relatively high.

The second source of deviation was that NHIS-based estimates suggest stable or increasing smoking prevalence among young adults and adolescents. Thus, prevalence in the original model differed from the CBO model, which shows a secular trend toward decreasing prevalence over time. The resolution to this issue was to decrease initiation rates across lower age ranges by lowering implied prevalence to 24-year-old prevalence and smoothing using a 10-year moving average process. The effect of this was a lowered prevalence among new birth cohorts that was a closer approximation to initial cohort and a prevalence pattern that approximated those of current 10- to 24-year-olds. This results in a new "steady-state" population prevalence of approximately 13-14%, which is lower than the current population-wide prevalence. Finally, the third source of deviation was that initial former smokers exhibited high relapse rates among older age groups (ages 50 or older), causing higher prevalence relative to the CBO model. The approach to resolve this issue was to utilize an exponential distribution, which decreased likelihood of relapse among initial former smokers, and relapse was eliminated for former smokers older than age 50.

3.7 Modeling cancer

Modeling cancer incidence and fatality

Cancers were modeled using an incidence and case-fatality rate approach, which tracked cancer incidence and mortality for each agent. Within the model, four categories of cancer were modeled: 1) trachea, lung, and bronchus, 2) colorectal cancer, 3) other cancers with smoking-attributable risk, and 4) other cancers with no smoking-attributable risk. Lung, bronchial and trachea site and morphology are: lung and bronchus, trachea, mediastinum and other respiratory organs. Colon and rectal site and morphology are: colon and rectum. All smoking-related site and morphology are: oral cavity and pharynx, esophagus, stomach, liver, pancreas, larynx, lung and bronchus, cervix uteri, urinary bladder, kidney and renal pelvis, acute myeloid leukemia. Site and morphology for cancers unrelated to smoking are: oral cavity and pharynx, esophagus, stomach, colon and rectum, liver, pancreas, larynx, lung and bronchus, cervix uteri, urinary bladder, kidney and renal pelvis, acute myeloid leukemia. These categories were used to sharpen adjustments by smoking behavior, aspirin effectiveness, and racial and ethnic differences.

Baseline incidence and case fatality rates by age and sex for each cancer category were estimated from Surveillance, Epidemiology, and End Results (SEER) data using SEER*Stat software [82]. Rates for colorectal cancer also were stratified by race/ethnicity. These baseline incidence and case-fatality rates were further adjusted by the age, sex and smoking status specific relative risks provided by the Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) tool maintained by the Center for Disease Control (CDC) [83]. Final incidence and case fatality rates are listed in **Tables B17-B20**.

Although each of the four cancer categories has unique risks, durations, and quality-adjusted life year (QALY) decrements, the basic algorithm employed to model disease incidence and burden is the same across all four categories. This algorithm is presented in **Figure B2**.

For each cancer category, the model first checks to see if the agent is experiencing a current cancer episode. If they are, their time in that state (i.e., dwell time) is checked to determine if the it has expired. If the dwell time has expired, the episode's terminal condition (death or resolution) is checked. If an episode's dwell time has not expired, disease and terminal condition-specific QALY decrements are applied and the episode continues.

If the agent is not in a current cancer episode, the model determines if a new cancer episode has begun. If it has, the eventual terminal condition of that state (death or resolution) is determined. The duration (dwell time) and QALY decrements of the cancer episodes are contained in **Table B21**.

Appendix B Table 16. Cancer Incidence and Case-Fatality Rates of Trachea, Lung, and Bronchus

	Female			Male		
	Incidence (per 100,000 adults)					
Age	**Never**	**Current**	**Former**	**Never**	**Current**	**Former**
35-39	0.0000083	0.00011	0.000022	0.0000074	0.00011	0.000032
40-44	0.000024	0.00032	0.000064	0.000022	0.00032	0.000097
45-49	0.000059	0.00079	0.00016	0.000056	0.00081	0.00025
50-54	0.00011	0.0015	0.0003	0.00013	0.0018	0.00055
55-59	0.00014	0.0027	0.00071	0.00021	0.0039	0.00094
60-64	0.00027	0.0052	0.0014	0.00043	0.0082	0.002
65-69	0.00042	0.01	0.0029	0.00066	0.019	0.0051
70-74	0.00055	0.013	0.0037	0.00098	0.028	0.0077
75-79	0.00063	0.015	0.0041	0.0014	0.032	0.0091
80-84	0.00059	0.014	0.0038	0.0015	0.034	0.0099
85+	0.00048	0.011	0.0031	0.0015	0.033	0.0094
	Mortality (case-fatality rate)					
35-39	0.093	1	0.25	0.11	1	0.47
40-44	0.11	1	0.29	0.11	1	0.5
45-49	0.12	1	0.31	0.13	1	0.55
50-54	0.13	1	0.34	0.13	1	0.56
55-59	0.089	1	0.45	0.11	1	0.5
60-64	0.1	1	0.51	0.13	1	0.59
65-69	0.095	1	0.65	0.11	1	0.89
70-74	0.098	1	0.67	0.12	1	0.96
75-79	0.11	1	0.67	0.14	1	0.93
80-84	0.11	1	0.71	0.16	1	1
85+	0.14	1	0.88	0.19	1	1

Sources: [82, 83]. Note: Never, Current, and Former columns refer to smoking status.

Appendix B Table 17. Colorectal Cancer Incidence Rates

		Female			Male		
		Incidence (per 100,000 adults)					
Race/ethnicity	Age	Never	Current	Former	Never	Current	Former
White	35-39	0.000067	0.000085	0.000083	0.000065	0.00011	0.000088
	40-44	0.00013	0.00016	0.00016	0.00012	0.00021	0.00016
	45-49	0.00022	0.00029	0.00028	0.00024	0.00041	0.00032
	50-54	0.0004	0.00051	0.00049	0.00046	0.00081	0.00063
	55-59	0.00044	0.00092	0.00057	0.00066	0.0012	0.00087
	60-64	0.00065	0.0014	0.00083	0.001	0.0019	0.0013
	65-69	0.0011	0.0022	0.0013	0.0015	0.0035	0.0022
	70-74	0.0014	0.003	0.0018	0.002	0.0048	0.003
	75-79	0.0019	0.0037	0.0025	0.0026	0.0056	0.0038
	80-84	0.0024	0.0046	0.003	0.003	0.0066	0.0044
	85+	0.0028	0.0054	0.0035	0.0035	0.0076	0.0051
African American	35-39	0.000081	0.0001	0.0001	0.000078	0.00014	0.00011
	40-44	0.00017	0.00022	0.00021	0.00017	0.0003	0.00023
	45-49	0.00031	0.0004	0.00039	0.00031	0.00054	0.00043
	50-54	0.00063	0.00081	0.00078	0.00064	0.0011	0.00088
	55-59	0.00065	0.0014	0.00083	0.00096	0.0018	0.0013
	60-64	0.00097	0.002	0.0012	0.0015	0.0027	0.0019
	65-69	0.0014	0.0029	0.0018	0.0019	0.0044	0.0028
	70-74	0.0018	0.0036	0.0022	0.0025	0.0059	0.0037
	75-79	0.0022	0.0043	0.0029	0.003	0.0065	0.0044
	80-84	0.0025	0.0049	0.0032	0.0036	0.0079	0.0053
	85+	0.0029	0.0057	0.0037	0.0038	0.0083	0.0056
Hispanic	35-39	0.000053	0.000068	0.000066	0.000052	0.00009	0.00007
	40-44	0.000098	0.00013	0.00012	0.000084	0.00015	0.00011
	45-49	0.00017	0.00021	0.0002	0.00018	0.00031	0.00025
	50-54	0.00024	0.00031	0.0003	0.00027	0.00047	0.00036
	55-59	0.00031	0.00064	0.00039	0.00043	0.00079	0.00056
	60-64	0.00051	0.0011	0.00065	0.00076	0.0014	0.001
	65-69	0.00076	0.0016	0.00096	0.00098	0.0023	0.0015
	70-74	0.0012	0.0024	0.0015	0.0015	0.0035	0.0022
	75-79	0.0014	0.0027	0.0018	0.0015	0.0032	0.0021
	80-84	0.0013	0.0026	0.0017	0.0036	0.0079	0.0053
	85+	0.0014	0.0028	0.0018	0.0022	0.0049	0.0033
Other	35-39	0.000065	0.000083	0.00008	0.000075	0.00013	0.0001
	40-44	0.00012	0.00015	0.00015	0.00015	0.00025	0.0002
	45-49	0.00022	0.00028	0.00027	0.00025	0.00044	0.00035
	50-54	0.0004	0.00051	0.0005	0.00048	0.00084	0.00065
	55-59	0.00045	0.00094	0.00058	0.00067	0.0012	0.00087
	60-64	0.00056	0.0012	0.00072	0.00094	0.0018	0.0012
	65-69	0.00094	0.0019	0.0012	0.0015	0.0034	0.0022
	70-74	0.0012	0.0024	0.0015	0.0018	0.0043	0.0027
	75-79	0.0014	0.0028	0.0018	0.0022	0.0049	0.0033
	80-84	0.0019	0.0036	0.0024	0.0025	0.0055	0.0037
	85+	0.0022	0.0042	0.0028	0.0027	0.0058	0.0039

Sources: [82, 83]. Note: Never, Current, and Former columns refer to smoking status.

Appendix B Table 18. Colorectal Case-Fatality Rates

		Female			Male		
		Mortality (Case-fatality rate)					
Race/ethnicity	Age	Never	Current	Former	Never	Current	Former
White	35-39	0.15	0.19	0.19	0.16	0.28	0.22
	40-44	0.15	0.2	0.19	0.16	0.28	0.22
	45-49	0.17	0.22	0.22	0.16	0.29	0.22
	50-54	0.16	0.2	0.19	0.16	0.27	0.21
	55-59	0.16	0.34	0.21	0.18	0.34	0.24
	60-64	0.18	0.37	0.23	0.2	0.37	0.26
	65-69	0.17	0.36	0.22	0.19	0.44	0.28
	70-74	0.19	0.39	0.24	0.19	0.45	0.28
	75-79	0.21	0.4	0.26	0.21	0.45	0.3
	80-84	0.25	0.48	0.31	0.25	0.54	0.36
	85+	0.36	0.7	0.46	0.33	0.73	0.49
African American	35-39	0.23	0.29	0.28	0.21	0.36	0.28
	40-44	0.19	0.25	0.24	0.2	0.35	0.27
	45-49	0.25	0.32	0.31	0.24	0.42	0.33
	50-54	0.19	0.25	0.24	0.2	0.34	0.27
	55-59	0.2	0.42	0.26	0.24	0.44	0.31
	60-64	0.21	0.43	0.26	0.25	0.46	0.32
	65-69	0.23	0.47	0.29	0.23	0.55	0.35
	70-74	0.25	0.51	0.31	0.25	0.58	0.37
	75-79	0.27	0.53	0.35	0.26	0.57	0.38
	80-84	0.33	0.64	0.42	0.31	0.68	0.46
	85+	0.46	0.89	0.58	0.41	0.88	0.59
Hispanic	35-39	0.091	0.12	0.11	0.33	0.57	0.44
	40-44	0.23	0.3	0.29	0.15	0.25	0.2
	45-49	0.21	0.26	0.25	0.26	0.45	0.35
	50-54	0.2	0.26	0.25	0.18	0.31	0.24
	55-59	0.18	0.37	0.23	0.28	0.52	0.36
	60-64	0.22	0.46	0.29	0.27	0.5	0.35
	65-69	0.26	0.53	0.32	0.25	0.58	0.37
	70-74	0.19	0.4	0.24	0.26	0.61	0.39
	75-79	0.34	0.66	0.43	0.29	0.64	0.43
	80-84	0.4	0.77	0.5	0.31	0.68	0.46
	85+	0.21	0.4	0.26	0.22	0.48	0.32
Other	35-39	0.19	0.24	0.24	0.18	0.31	0.24
	40-44	0.19	0.24	0.23	0.17	0.3	0.24
	45-49	0.17	0.21	0.21	0.19	0.33	0.26
	50-54	0.14	0.18	0.17	0.14	0.24	0.19
	55-59	0.15	0.32	0.19	0.2	0.38	0.27
	60-64	0.18	0.37	0.23	0.19	0.35	0.25
	65-69	0.14	0.29	0.18	0.19	0.44	0.28
	70-74	0.18	0.37	0.23	0.21	0.5	0.32
	75-79	0.21	0.4	0.26	0.22	0.48	0.32
	80-84	0.25	0.49	0.32	0.28	0.62	0.42
	85+	0.38	0.73	0.48	0.37	0.81	0.54

Sources: [82, 83]. Note: Never, Current, and Former columns refer to smoking status.

Appendix B Table 19. Incidence and Case-Fatality of Other Cancers With Smoking-Attributable Risk

	Female			Male		
	Incidence (per 100,000 adults)					
Age	Never	Current	Former	Never	Current	Former
35-39	0.00033	0.00042	0.0004	0.00024	0.00041	0.00032
40-44	0.00053	0.00068	0.00066	0.00051	0.00089	0.0007
45-49	0.00087	0.0011	0.0011	0.0011	0.0019	0.0015
50-54	0.0014	0.0018	0.0018	0.0021	0.0036	0.0028
55-59	0.0018	0.0037	0.0023	0.0033	0.0062	0.0044
60-64	0.0028	0.0058	0.0036	0.0053	0.0098	0.0069
65-69	0.0044	0.0091	0.0056	0.0075	0.018	0.011
70-74	0.0058	0.012	0.0073	0.01	0.023	0.015
75-79	0.007	0.013	0.0088	0.012	0.027	0.018
80-84	0.0076	0.015	0.0096	0.014	0.03	0.02
85+	0.0076	0.015	0.0096	0.014	0.031	0.02
	Mortality (Case-fatality rate)					
35-39	0.17	0.22	0.22	0.22	0.37	0.29
40-44	0.23	0.29	0.28	0.24	0.41	0.32
45-49	0.28	0.35	0.34	0.27	0.48	0.37
50-54	0.29	0.37	0.36	0.29	0.51	0.4
55-59	0.28	0.58	0.36	0.32	0.59	0.42
60-64	0.31	0.64	0.39	0.34	0.64	0.45
65-69	0.33	0.67	0.41	0.33	0.77	0.49
70-74	0.35	0.72	0.44	0.33	0.78	0.49
75-79	0.37	0.71	0.47	0.34	0.74	0.5
80-84	0.4	0.77	0.51	0.36	0.79	0.53
85+	0.48	0.93	0.61	0.43	0.93	0.62

Sources: [82, 83]. Note: Never, Current, and Former columns refer to smoking status.

Appendix B Table 20. Incidence and Case-Fatality of Other Cancers With No Smoking-Attributable Risk

	Female			Male		
	Incidence (per 100,000 adults)					
Age	Never	Current	Former	Never	Current	Former
35-39	0.00036	0.00036	0.00036	0.00029	0.00029	0.00029
40-44	0.00059	0.00059	0.00059	0.00063	0.00063	0.00063
45-49	0.00097	0.00097	0.00097	0.0013	0.0013	0.0013
50-54	0.0016	0.0016	0.0016	0.0026	0.0026	0.0026
55-59	0.0023	0.0023	0.0023	0.0042	0.0042	0.0042
60-64	0.0035	0.0035	0.0035	0.0064	0.0064	0.0064
65-69	0.0053	0.0053	0.0053	0.0093	0.0093	0.0093
70-74	0.0069	0.0069	0.0069	0.012	0.012	0.012
75-79	0.0084	0.0084	0.0084	0.015	0.015	0.015
80-84	0.0092	0.0092	0.0092	0.016	0.016	0.016
85+	0.009	0.009	0.009	0.016	0.016	0.016
	Mortality (Case-fatality rate)					
35-39	0.19	0.19	0.19	0.26	0.26	0.26
40-44	0.25	0.25	0.25	0.29	0.29	0.29
45-49	0.31	0.31	0.31	0.34	0.34	0.34
50-54	0.32	0.32	0.32	0.36	0.36	0.36
55-59	0.36	0.36	0.36	0.4	0.4	0.4
60-64	0.39	0.39	0.39	0.41	0.41	0.41
65-69	0.39	0.39	0.39	0.4	0.4	0.4
70-74	0.42	0.42	0.42	0.4	0.4	0.4
75-79	0.45	0.45	0.45	0.41	0.41	0.41
80-84	0.48	0.48	0.48	0.43	0.43	0.43
85+	0.57	0.57	0.57	0.49	0.49	0.49

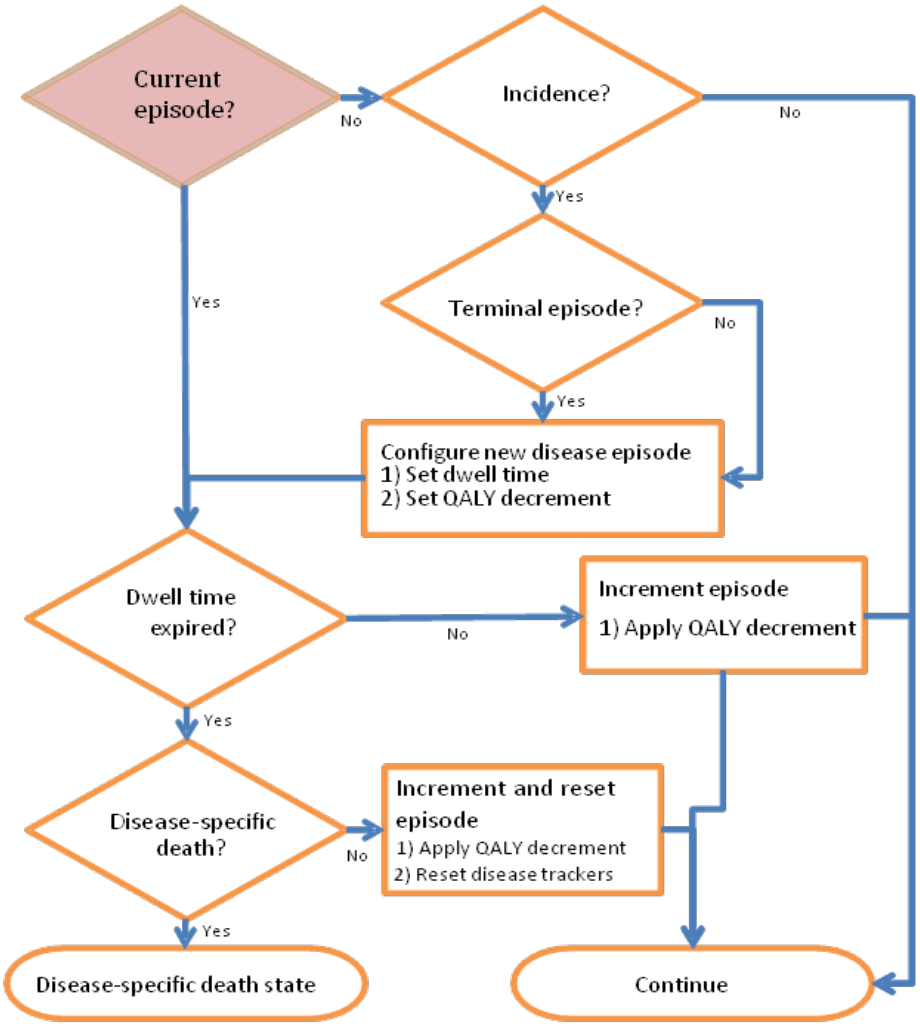
Sources: [83]. Note: Never, Current, and Former columns refer to smoking status.

Appendix B Table 21. Duration and QALY Decrement for Cancer Episodes

Cancers	Average Time from DX to death	Duration for QoL reduction if no death	Quality of life Decrement per yr
Trachea, Lung, Bronchus	2	5	0.3
Colorectal Cancer	2.3	5	0.3
Other SAMMEC Cancers	4.7	5	0.2
Other Cancers	4.7	5	0.3

Source: Author assumption. Note: Fast growing cancers are treated as an acute condition (decrement = .3/year) and others as chronic (decrement = .2/year).

Appendix B Figure 2. Algorithm for Modeling Cancer Incidence and Case Fatality



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Addendum

This addendum provides additional data not available when this evidence report was finalized. A "bridge search" by the systematic evidence review teams identified newly published data from the Japanese Primary Prevention Project (JPPP) trial (Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. *JAMA*. 2014;312:2510-20). These data are incorporated into the journal manuscripts based on the systematic evidence reviews (Chubak J, Whitlock EP, Williams SB, et al. Aspirin for the prevention of cancer incidence and mortality: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2015. [In press]; Guirguis-Blake JM, Evans CV, Senger CA, et al. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2015. [In press]; Whitlock EP, Burda BU, Williams SB. Bleeding risks with aspirin use for primary prevention in adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann of Intern Med* 2015. [In press]), and a supplemental analysis using these new data is included in the manuscript derived from this report (Dehmer SP, Maciosek MV, Flottemesch TJ. Aspirin for the primary prevention of cardiovascular disease and colorectal cancer: a decision analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2015. [In press]). **Addendum Table 1** compares the key benefit and harm parameters between the base-case analysis and the supplemental analysis that includes evidence from the JPPP trial. **Addendum Tables 2-12** contain comprehensive results from the supplemental analysis. **Addendum Tables 2-4** correspond with **Tables 4-6** of the base-case analysis described in this report, and **Addendum Tables 5-12** correspond with **Appendix A Tables 5-12**.

Addendum Table 1. Comparison of Benefit and Harm Parameters Between Base and Supplemental Cases

Parameter	Base case	Supplemental case with JPPP
Benefits		
All cancer incidence/death, relative risk	1.00	1.00
CRC death, relative risk	1.00	1.00
CRC incidence (1-10 years), relative risk	1.00	1.00
CRC incidence (>10 years), relative risk	0.60	0.60
CVD death, relative risk	1.00	1.00
Ischemic stroke (non-fatal), relative risk	0.82	0.86
Myocardial infarction (non-fatal), relative risk	0.85	0.83
Harms		
GI bleeding (major), relative risk	1.59	1.58
Hemorrhagic stroke, relative risk	1.14	1.27

Notes: CRC=colorectal cancer; CVD=cardiovascular disease; GI=gastrointestinal. JPPP=Japanese Primary Prevention Project. The base case parameters are as described in **Table 1** and in the text of this report. The supplemental case with JPPP parameters are sourced from the systematic evidence review manuscripts, as described in the manuscript derived from this report.

Addendum Table 2. Lifetime Net Benefit of Aspirin for Men and Women, Supplemental Case

% 10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Men				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	28.0 (18.6 to 37.4)	13.2 (5.2 to 21.2)	N/A	N/A
5	48.9 (39.6 to 58.3)	15.3 (7.1 to 23.4)	-5.7 (-12.3 to 0.8)	N/A
10	71.0 (61.3 to 80.6)	33.3 (24.6 to 42.1)	-2.0 (-9.2 to 5.2)	-15.1 (-20.3 to -9.9)
15	82.8 (73.1 to 92.5)	39.5 (30.9 to 48.1)	9.6 (2.7 to 16.5)	-18.0 (-23.3 to -12.8)
20	80.1 (70.2 to 90.0)	60.5 (52.3 to 68.7)	11.6 (4.6 to 18.6)	-22.5 (-27.8 to -17.3)
	QALYs per 1000 persons (95% Confidence Interval)			
1	51.7 (43.0 to 60.5)	36.8 (29.5 to 44.1)	N/A	N/A
5	74.1 (65.6 to 82.7)	40.0 (32.6 to 47.5)	16.1 (10.2 to 22.0)	N/A
10	97.2 (88.4 to 105.9)	58.8 (51.0 to 66.6)	18.0 (11.4 to 24.5)	-1.0 (-5.7 to 3.6)
15	107.9 (99.0 to 116.7)	64.4 (56.5 to 72.3)	30.9 (24.6 to 37.1)	-3.1 (-7.9 to 1.6)
20	105.7 (96.6 to 114.8)	83.4 (75.8 to 91.0)	31.8 (25.4 to 38.2)	-6.2 (-10.9 to -1.5)
Women				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	3.2 (-6.3 to 12.6)	-9.6 (-18.3 to -0.9)	-18.2 (-26.1 to -10.3)	N/A
5	41.7 (30.8 to 52.6)	10.0 (0.7 to 19.2)	-12.7 (-19.9 to -5.5)	-23.4 (-29.2 to -17.6)
10	59.0 (48.5 to 69.4)	21.9 (12.7 to 31.2)	-1.2 (-8.5 to 6.1)	-25.1 (-30.7 to -19.5)
15	57.3 (46.3 to 68.4)	33.4 (24.2 to 42.6)	1.7 (-5.5 to 8.8)	-22.3 (-28.0 to -16.6)
20	67.7 (57.3 to 78.1)	46.3 (37.3 to 55.2)	4.8 (-2.5 to 12.1)	-26.1 (-31.8 to -20.4)
	QALYs per 1000 persons (95% Confidence Interval)			
1	36.6 (27.7 to 45.4)	21.8 (13.9 to 29.8)	7.4 (0.2 to 14.6)	N/A
5	78.4 (68.4 to 88.4)	45.0 (36.3 to 53.6)	16.4 (9.8 to 23.1)	-4.4 (-9.7 to 0.8)
10	96.9 (87.2 to 106.6)	62.1 (53.6 to 70.7)	28.4 (21.6 to 35.3)	-4.4 (-9.6 to 0.8)
15	98.4 (88.3 to 108.6)	71.6 (63.1 to 80.2)	32.4 (25.8 to 39.1)	-1.5 (-6.8 to 3.8)
20	106.5 (96.9 to 116.2)	83.3 (75.0 to 91.6)	36.0 (29.3 to 42.7)	-2.7 (-7.9 to 2.5)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample.

Addendum Table 3. Net Benefit of Aspirin Over 20 Years for Men and Women, Supplemental Case

% 10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Men				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	-1.8 (-3.1 to -0.4)	-5.5 (-7.7 to -3.3)	N/A	N/A
5	-2.7 (-4.5 to -0.8)	-6.2 (-8.6 to -3.8)	-11.1 (-13.9 to -8.3)	N/A
10	-1.9 (-4.1 to 0.4)	-2.8 (-5.8 to 0.1)	-10.7 (-14.2 to -7.3)	-16.2 (-19.9 to -12.5)
15	0.7 (-1.7 to 3.0)	-2.2 (-5.4 to 1.0)	-5.3 (-8.6 to -2.0)	-18.1 (-22.0 to -14.3)
20	1.4 (-0.9 to 3.7)	7.4 (4.1 to 10.6)	-7.5 (-11.4 to -3.5)	-22.3 (-26.5 to -18.2)
	QALYs per 1000 persons (95% Confidence Interval)			
1	0.1 (-1.4 to 1.6)	0.1 (-2.2 to 2.3)	N/A	N/A
5	4.2 (2.2 to 6.1)	2.6 (0.2 to 5.1)	0.1 (-2.6 to 2.8)	N/A
10	8.7 (6.4 to 11.0)	10.1 (7.1 to 13.0)	1.9 (-1.4 to 5.2)	-4.7 (-8.1 to -1.3)
15	11.6 (9.2 to 14.1)	12.8 (9.6 to 15.9)	10.1 (6.9 to 13.4)	-5.7 (-9.3 to -2.1)
20	14.2 (11.7 to 16.6)	23.6 (20.5 to 26.8)	8.8 (5.1 to 12.5)	-8.4 (-12.1 to -4.6)
Women				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	-1.7 (-2.8 to -0.7)	-5.3 (-7.0 to -3.6)	-7.9 (-10.2 to -5.6)	N/A
5	-2.1 (-3.7 to -0.5)	-7.8 (-10.4 to -5.3)	-10.3 (-13.0 to -7.5)	-17.1 (-20.3 to -13.8)
10	-1.2 (-2.9 to 0.6)	-6.4 (-9.4 to -3.5)	-10.5 (-13.8 to -7.2)	-20.5 (-24.3 to -16.7)
15	0.4 (-1.4 to 2.2)	-3.6 (-6.5 to -0.8)	-11.0 (-14.4 to -7.6)	-22.2 (-26.2 to -18.3)
20	-0.6 (-2.5 to 1.3)	-2.6 (-5.6 to 0.4)	-7.9 (-11.6 to -4.2)	-24.3 (-28.6 to -20.1)
	QALYs per 1000 persons (95% Confidence Interval)			
1	1.4 (0.1 to 2.7)	-0.2 (-2.0 to 1.6)	-0.7 (-3.0 to 1.6)	N/A
5	5.2 (3.4 to 7.1)	4.2 (1.6 to 6.8)	2.2 (-0.5 to 5.0)	-6.1 (-9.1 to -3.1)
10	8.7 (6.8 to 10.7)	10.2 (7.2 to 13.2)	6.6 (3.2 to 10.0)	-6.1 (-9.8 to -2.5)
15	11.3 (9.3 to 13.3)	15.0 (12.0 to 18.0)	9.3 (5.9 to 12.8)	-6.4 (-10.1 to -2.7)
20	10.3 (8.2 to 12.3)	16.8 (13.7 to 19.9)	13.0 (9.4 to 16.7)	-5.5 (-9.4 to -1.6)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample.

Addendum Table 4. Net Benefit of Aspirin Over 10 Years for Men and Women, Supplemental Case

% 10-yr CVD Risk	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Men				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	-0.5 (-0.7 to -0.2)	-1.0 (-1.4 to -0.5)	N/A	N/A
5	-0.7 (-1.1 to -0.3)	-1.8 (-2.3 to -1.2)	-3.2 (-4.1 to -2.3)	N/A
10	-1.1 (-1.7 to -0.6)	-2.1 (-2.7 to -1.5)	-4.2 (-5.2 to -3.2)	-6.5 (-7.7 to -5.2)
15	-1.3 (-1.9 to -0.7)	-2.6 (-3.5 to -1.8)	-3.9 (-4.9 to -2.9)	-6.1 (-7.3 to -4.9)
20	-0.8 (-1.3 to -0.3)	-1.1 (-1.9 to -0.2)	-5.1 (-6.5 to -3.7)	-9.8 (-11.3 to -8.2)
	QALYs per 1000 persons (95% Confidence Interval)			
1	-0.8 (-1.2 to -0.5)	-1.1 (-1.7 to -0.6)	N/A	N/A
5	-0.1 (-0.6 to 0.4)	-1.4 (-2.0 to -0.7)	-2.8 (-3.7 to -1.9)	N/A
10	0.5 (-0.1 to 1.2)	-0.4 (-1.1 to 0.4)	-2.9 (-4.0 to -1.8)	-4.9 (-6.1 to -3.7)
15	0.7 (0.0 to 1.3)	-0.0 (-1.0 to 0.9)	-1.3 (-2.3 to -0.3)	-4.5 (-5.7 to -3.3)
20	2.0 (1.4 to 2.6)	3.0 (2.1 to 3.9)	-1.7 (-3.0 to -0.4)	-6.8 (-8.3 to -5.4)
Women				
	Net Life Years per 1000 persons (95% Confidence Interval)			
1	-0.3 (-0.5 to -0.0)	-0.9 (-1.2 to -0.5)	-2.4 (-3.2 to -1.7)	N/A
5	-0.7 (-1.1 to -0.3)	-2.2 (-2.9 to -1.5)	-2.7 (-3.5 to -2.0)	-3.4 (-4.2 to -2.6)
10	-0.6 (-1.0 to -0.2)	-2.5 (-3.4 to -1.7)	-3.2 (-4.1 to -2.2)	-5.0 (-6.1 to -3.9)
15	-0.3 (-0.6 to 0.1)	-2.0 (-2.8 to -1.2)	-4.4 (-5.4 to -3.3)	-6.6 (-7.9 to -5.4)
20	-0.7 (-1.2 to -0.3)	-2.3 (-3.1 to -1.5)	-4.9 (-6.1 to -3.7)	-7.8 (-9.2 to -6.4)
	QALYs per 1000 persons (95% Confidence Interval)			
1	-0.3 (-0.6 to 0.1)	-1.0 (-1.5 to -0.5)	-2.6 (-3.3 to -1.8)	N/A
5	0.1 (-0.4 to 0.6)	-0.8 (-1.6 to -0.1)	-1.5 (-2.3 to -0.7)	-2.9 (-3.8 to -2.1)
10	0.9 (0.4 to 1.5)	0.1 (-0.8 to 1.1)	-0.4 (-1.5 to 0.6)	-3.1 (-4.2 to -2.0)
15	1.7 (1.2 to 2.2)	1.6 (0.6 to 2.5)	0.1 (-1.1 to 1.2)	-4.0 (-5.2 to -2.7)
20	1.2 (0.6 to 1.8)	1.5 (0.6 to 2.5)	0.3 (-0.9 to 1.6)	-3.6 (-5.0 to -2.2)

Notes: CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the original modeled population sample.

Addendum Table 5. Detailed Benefits and Harms From Aspirin Use for Men Aged 40-49 Years, Supplemental Case

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	21.6	6.4	33.3	3.7	15.0	3.4	31.9	2.9	1.8	2.6	28.0	51.7	17.1
5	23.8	7.6	37.4	4.1	14.8	3.7	28.5	2.5	1.5	2.4	48.9	74.1	25.4
10	28.1	8.0	43.6	4.6	15.4	3.7	25.0	2.1	1.4	2.0	71.0	97.2	36.5
15	31.1	8.5	48.0	5.4	13.9	3.3	23.7	2.1	1.4	1.9	82.8	107.9	41.5
20	32.6	8.4	49.6	5.5	13.2	3.1	22.8	2.2	1.1	2.0	80.1	105.7	43.4
20-year outcomes													
1	7.7	1.1	9.1	0.1	2.5	0.5	10.2	1.1	0.1	0.7	-1.8	0.1	0.4
5	12.2	2.5	15.6	0.4	3.7	0.7	12.4	1.0	0.3	0.7	-2.7	4.2	6.2
10	16.8	3.5	21.6	0.8	4.7	0.8	11.2	1.0	0.2	0.9	-1.9	8.7	14.9
15	20.1	3.8	25.8	1.1	4.1	0.8	10.8	1.0	0.2	0.8	0.7	11.6	19.1
20	21.7	4.4	28.5	1.5	4.3	0.8	10.6	1.1	0.2	0.9	1.4	14.2	22.5
10-year outcomes													
1	2.6	0.2	2.9	0.0	0.0	0.0	3.5	0.4	0.1	0.1	-0.5	-0.8	-1.1
5	5.2	0.9	6.2	0.0	0.0	0.0	4.9	0.5	0.1	0.2	-0.7	-0.1	0.8
10	8.2	1.3	9.8	0.1	0.0	0.0	5.0	0.5	0.1	0.3	-1.1	0.5	4.3
15	10.1	1.5	12.0	0.1	0.0	0.0	4.6	0.5	0.1	0.3	-1.3	0.7	7.0
20	11.3	1.9	13.6	0.1	0.0	0.0	4.8	0.5	0.0	0.3	-0.8	2.0	8.4

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Addendum Table 6. Detailed Benefits and Harms From Aspirin Use for Women Aged 40-49 Years, Supplemental Case

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	11.1	10.2	25.7	2.7	14.1	3.5	25.8	3.9	1.9	3.3	3.2	36.6	12.9
5	14.1	11.8	32.1	4.0	15.5	4.3	21.0	3.7	1.5	3.3	41.7	78.4	26.9
10	15.9	12.3	35.4	4.1	16.2	4.1	20.8	3.0	1.3	2.7	59.0	96.9	32.0
15	17.2	13.7	38.6	4.8	14.9	3.4	19.1	2.9	1.2	2.9	57.3	98.4	36.3
20	17.7	13.0	38.5	4.5	15.5	4.0	18.5	2.5	1.4	2.2	67.7	106.5	37.5
20-year outcomes													
1	3.8	1.8	5.9	0.1	2.6	0.4	7.8	1.1	0.1	0.6	-1.7	1.4	-0.4
5	6.4	3.5	10.4	0.3	3.4	0.8	7.0	1.2	0.1	0.8	-2.1	5.2	5.9
10	8.2	4.4	13.6	0.3	3.9	0.7	7.5	1.1	0.1	0.8	-1.2	8.7	9.2
15	9.3	5.0	15.4	0.6	3.6	0.6	7.0	1.1	0.1	0.9	0.4	11.3	11.5
20	9.9	4.3	15.4	0.5	4.0	0.6	6.6	1.1	0.2	0.7	-0.6	10.3	12.2
10-year outcomes													
1	1.3	0.5	1.8	0.0	0.0	0.0	2.8	0.3	0.0	0.0	-0.3	-0.3	-1.3
5	2.8	1.2	4.1	0.0	0.0	0.0	2.7	0.5	0.0	0.2	-0.7	0.1	1.0
10	4.1	1.7	6.0	0.0	0.0	0.0	3.0	0.4	0.0	0.2	-0.6	0.9	2.6
15	4.4	2.0	6.5	0.1	0.0	0.0	2.6	0.4	0.0	0.1	-0.3	1.7	3.6
20	4.9	1.7	6.9	0.1	0.0	0.0	2.5	0.4	0.0	0.2	-0.7	1.2	4.1

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Addendum Table 7. Detailed Benefits and Harms From Aspirin Use for Men Aged 50-59 Years, Supplemental Case

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	17.0	6.1	27.7	3.2	14.0	3.3	33.9	2.7	2.1	2.2	13.2	36.8	8.2
5	19.4	7.0	31.6	3.7	14.1	3.5	30.0	3.0	2.0	2.7	15.3	40.0	16.3
10	22.5	8.4	37.2	4.1	13.9	3.0	28.4	2.3	1.8	2.1	33.3	58.8	24.5
15	26.7	8.6	43.4	5.4	12.1	2.3	26.0	2.8	1.5	2.5	39.5	64.4	32.2
20	28.6	9.2	46.2	5.5	12.2	2.7	24.8	2.1	1.2	1.9	60.5	83.4	37.0
20-year outcomes													
1	8.2	2.3	10.9	0.3	4.3	0.7	16.5	1.3	0.5	1.0	-5.5	0.1	-2.4
5	11.7	3.3	15.9	0.7	5.7	1.1	17.2	1.7	0.5	1.4	-6.2	2.6	3.4
10	16.4	4.6	23.1	1.4	6.8	1.2	18.2	1.6	0.5	1.4	-2.8	10.1	11.5
15	20.3	5.8	29.4	2.1	6.3	0.9	17.2	1.8	0.5	1.6	-2.2	12.8	18.8
20	23.2	6.3	33.9	2.9	7.0	1.3	17.0	1.6	0.4	1.4	7.4	23.6	25.2
10-year outcomes													
1	2.9	0.7	3.6	0.0	0.0	0.0	7.1	0.5	0.1	0.2	-1.0	-1.1	-3.9
5	5.2	1.0	6.2	0.0	0.0	0.0	7.9	0.7	0.2	0.4	-1.8	-1.4	-2.3
10	8.0	1.8	10.1	0.2	0.0	0.0	8.5	0.8	0.2	0.6	-2.1	-0.4	1.0
15	10.5	2.4	13.5	0.3	0.0	0.0	8.4	1.0	0.2	0.7	-2.6	0.0	4.4
20	13.4	3.2	17.5	0.7	0.0	0.0	8.6	0.9	0.1	0.6	-1.1	3.0	8.7

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Addendum Table 8. Detailed Benefits and Harms From Aspirin Use for Women Aged 50-59 Years, Supplemental Case

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	9.4	9.4	22.2	2.5	13.7	3.4	25.6	3.8	2.1	3.3	-9.6	21.8	9.0
5	12.2	11.3	28.7	3.6	14.1	3.6	23.9	3.6	1.8	3.3	10.0	45.0	18.9
10	14.8	13.7	35.8	3.9	13.9	3.6	20.9	3.5	1.4	3.1	21.9	62.1	29.3
15	15.0	14.3	36.7	4.7	13.5	3.4	20.0	3.4	1.3	3.1	33.4	71.6	31.5
20	15.2	14.4	36.6	4.4	13.2	3.6	18.4	2.9	1.4	2.6	46.3	83.3	33.1
20-year outcomes													
1	4.2	2.5	7.0	0.1	3.7	0.6	10.8	1.6	0.3	1.0	-5.3	-0.2	-1.6
5	7.0	5.4	13.5	0.5	5.1	0.8	12.7	1.8	0.3	1.4	-7.8	4.2	4.5
10	9.9	7.7	19.6	1.2	6.1	1.2	12.3	2.2	0.3	1.8	-6.4	10.2	12.4
15	10.6	8.6	22.0	1.5	6.0	1.1	12.4	2.0	0.3	1.7	-3.6	15.0	15.1
20	10.9	8.9	22.6	1.9	6.1	1.2	10.8	1.8	0.3	1.6	-2.6	16.8	17.9
10-year outcomes													
1	1.5	0.7	2.2	0.0	0.0	0.0	4.0	0.5	0.1	0.2	-0.9	-1.0	-2.3
5	3.2	2.1	5.5	0.0	0.0	0.0	5.5	0.8	0.1	0.4	-2.2	-0.8	-0.7
10	5.2	3.1	8.7	0.1	0.0	0.0	5.3	1.0	0.1	0.6	-2.5	0.1	2.6
15	5.9	3.8	10.2	0.2	0.0	0.0	5.7	1.0	0.1	0.6	-2.0	1.6	3.7
20	5.6	4.1	10.3	0.2	0.0	0.0	5.0	0.9	0.1	0.7	-2.3	1.5	4.6

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Addendum Table 9. Detailed Benefits and Harms From Aspirin Use for Men Aged 60-69 Years, Supplemental Case

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	14.9	6.4	25.6	3.0	12.1	2.8	33.6	2.6	2.3	2.3	-5.7	16.1	4.6
10	15.9	6.6	26.6	3.3	11.2	2.6	31.4	3.1	2.2	2.7	-2.0	18.0	6.7
15	18.6	8.0	32.2	4.0	10.4	2.4	29.8	2.4	2.2	2.2	9.6	30.9	14.3
20	20.1	8.4	34.2	4.5	9.1	1.9	26.7	2.7	2.2	2.4	11.6	31.8	18.4
20-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	10.3	3.9	15.7	0.7	7.2	1.2	24.9	1.9	1.0	1.7	-11.1	0.1	-3.2
10	13.0	4.7	19.5	1.4	7.4	1.4	24.8	2.4	1.1	2.1	-10.7	1.9	1.0
15	15.5	6.4	25.1	2.3	7.3	1.5	24.8	2.0	1.3	1.8	-5.3	10.1	7.9
20	17.5	7.1	28.3	2.9	6.5	1.0	22.8	2.4	1.5	2.1	-7.5	8.8	12.5
10-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	4.1	1.4	5.7	0.1	0.0	0.0	11.7	1.0	0.4	0.6	-3.2	-2.8	-6.9
10	6.6	2.1	9.0	0.2	0.0	0.0	12.4	1.3	0.3	0.9	-4.2	-2.9	-4.5
15	8.6	2.9	12.2	0.4	0.0	0.0	13.7	1.1	0.4	0.8	-3.9	-1.3	-2.3
20	10.3	3.5	14.8	0.4	0.0	0.0	13.0	1.4	0.4	1.1	-5.1	-1.7	0.8

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Addendum Table 10. Detailed Benefits and Harms From Aspirin Use for Women Aged 60-69 Years, Supplemental Case

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	7.2	8.8	18.4	1.8	12.5	3.5	27.2	4.2	2.5	3.6	-18.2	7.4	1.2
5	9.0	10.5	23.3	2.5	11.1	2.9	24.6	3.6	2.2	3.2	-12.7	16.4	8.7
10	10.1	11.6	26.7	3.1	10.5	2.7	23.0	3.2	2.1	2.8	-1.2	28.4	14.1
15	11.0	12.9	29.7	3.9	9.3	2.6	21.6	3.4	2.0	3.0	1.7	32.4	18.0
20	11.1	13.0	30.3	4.4	9.7	2.7	21.7	3.3	2.1	2.9	4.8	36.0	19.4
20-year outcomes													
1	4.0	3.6	8.0	0.3	5.5	0.9	16.7	2.2	0.6	1.6	-7.9	-0.7	-5.1
5	6.3	6.1	13.6	0.8	5.9	1.0	17.3	2.4	1.0	1.9	-10.3	2.2	0.6
10	7.9	8.1	18.4	1.4	6.0	1.1	17.3	2.5	1.1	2.1	-10.5	6.6	6.0
15	9.1	9.7	22.1	2.0	5.8	1.3	17.1	2.7	1.3	2.3	-11.0	9.3	10.2
20	8.9	10.0	22.6	2.5	6.2	1.2	17.4	2.7	1.3	2.4	-7.9	13.0	11.2
10-year outcomes													
1	1.2	0.9	2.2	0.0	0.0	0.0	7.1	0.7	0.3	0.3	-2.4	-2.6	-5.6
5	3.1	2.2	5.4	0.0	0.0	0.0	8.3	1.0	0.2	0.5	-2.7	-1.5	-3.8
10	4.3	3.6	8.4	0.2	0.0	0.0	9.2	1.2	0.3	0.8	-3.2	-0.4	-1.8
15	5.1	4.8	10.8	0.4	0.0	0.0	9.1	1.5	0.3	1.1	-4.4	0.1	0.6
20	5.4	5.4	11.7	0.4	0.0	0.0	9.2	1.6	0.3	1.1	-4.9	0.3	1.3

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Addendum Table 11. Detailed Benefits and Harms From Aspirin Use for Men Aged 70-79 Years, Supplemental Case

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-	-
10	11.9	6.1	21.6	2.7	7.9	2.1	32.7	2.2	3.4	1.9	-15.1	-1.0	-2.6
15	12.8	6.5	22.5	2.5	6.9	1.7	30.6	2.3	3.3	2.0	-18.0	-3.1	-1.0
20	13.2	7.2	24.2	3.0	6.8	1.6	30.7	2.6	3.4	2.3	-22.5	-6.2	0.6
20-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-	-
10	10.9	5.4	18.8	2.0	6.6	1.6	30.6	2.0	3.1	1.7	-16.2	-4.7	-5.3
15	11.9	6.0	20.5	2.0	5.6	1.3	29.0	2.1	3.0	1.8	-18.1	-5.7	-3.0
20	12.5	6.6	22.1	2.6	5.9	1.3	29.6	2.4	3.1	2.1	-22.3	-8.4	-1.4
10-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-	-
10	5.7	2.3	8.7	0.4	0.0	0.0	18.9	1.2	1.2	1.0	-6.5	-4.9	-11.1
15	6.7	2.8	10.0	0.5	0.0	0.0	18.8	1.2	1.1	1.0	-6.1	-4.5	-9.6
20	7.7	3.5	12.0	0.5	0.1	0.0	20.5	1.6	1.5	1.4	-9.8	-6.8	-9.6

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).

Addendum Table 12. Detailed Benefits and Harms From Aspirin Use for Women Aged 70-79 Years, Supplemental Case

	Benefits from aspirin						Harms from aspirin				Net Balance		
10-yr CVD Risk	Myocardial Infarction	Ischemic Stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	GI Bleeds	Hemorrhagic Stroke	GI Bleed Deaths	H. Stroke Deaths	Net Life Years	Net QALYs	Net Events Prevented
%	(Prevented events per 1,000 persons)						(Incurred events per 1,000 persons)				(Benefits - harms)		
Lifetime outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	6.0	7.9	16.2	1.4	8.4	2.6	26.6	3.0	2.9	2.5	-23.4	-4.4	-3.6
10	7.1	8.8	19.1	2.0	7.9	2.3	23.5	3.5	2.7	3.0	-25.1	-4.4	1.9
15	7.5	9.8	20.5	2.0	7.3	2.4	22.9	3.2	2.7	2.7	-22.3	-1.5	3.7
20	8.6	10.6	22.8	2.5	7.2	2.1	21.4	3.3	2.8	3.0	-26.1	-2.7	7.8
20-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	4.8	5.5	11.6	0.7	5.6	1.5	23.0	2.4	2.2	1.9	-17.1	-6.1	-7.5
10	6.1	7.1	15.2	1.3	5.6	1.6	20.9	3.0	2.2	2.5	-20.5	-6.1	-1.7
15	6.5	8.1	16.6	1.5	5.6	1.7	20.6	2.9	2.4	2.5	-22.2	-6.4	0.1
20	7.8	9.5	19.9	1.8	5.9	1.6	19.7	3.0	2.6	2.7	-24.3	-5.5	4.9
10-year outcomes													
1	-	-	-	-	-	-	-	-	-	-	-	-	-
5	2.1	1.7	3.9	0.0	0.0	0.0	12.3	1.0	0.4	0.6	-3.4	-2.9	-9.3
10	3.4	3.2	7.1	0.2	0.0	0.0	12.0	1.4	0.7	1.0	-5.0	-3.1	-6.1
15	3.7	3.9	8.0	0.2	0.0	0.0	12.2	1.6	0.9	1.2	-6.6	-4.0	-5.5
20	4.4	5.1	10.2	0.4	0.0	0.0	11.9	1.7	1.1	1.3	-7.8	-3.6	-2.9

Notes: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; H. Stroke=hemorrhagic stroke; QALY=quality-adjusted life year; yr=year. The 10-year CVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). The GI bleed and hemorrhagic stroke columns include both fatal and non-fatal events. Net events prevented are defined by the net of benefit and harm events, or: (Non-fatal CVD events + CVD deaths + CRC cases) – (GI bleeds + hemorrhagic stroke).