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Screening for Obstructive Sleep Apnea in Adults: An Evidence Review for the U.S. Preventive Services Task Force

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Structured Abstract

Purpose: To systematically review the evidence on screening and treating asymptomatic adults or those with unrecognized symptoms for obstructive sleep apnea (OSA).

Data Sources: PubMed/MEDLINE, the Cochrane Library, EMBASE, and trial registries through October 2015; reference lists of retrieved articles; outside experts; and reviewers, with surveillance of the literature through October 5, 2016.

Study Selection: Two investigators independently selected English-language studies using a priori criteria. Eligible studies included randomized, controlled trials (RCTs) of screening for or treatment of OSA, studies evaluating accuracy of screening questionnaires or clinical prediction tools in asymptomatic adults or persons with unrecognized symptoms of OSA, systematic reviews (and studies published after eligible systematic reviews) evaluating diagnostic accuracy or reliability of portable monitors (PMs), and prospective cohort studies (≥1 year) evaluating the association between apnea-hypopnea index (AHI) and health outcomes among community-based participants that adjusted for potential confounding through multivariable analyses.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality for all included studies using predefined criteria.

Data Synthesis: We included 110 studies. No RCTs compared screening with no screening. The only screening approach for which we found two eligible studies reporting accuracy was the Multivariable Apnea Prediction (MVAP) score followed by home PM testing; for detecting severe OSA syndrome (OSAS) (AHI ≥30 and Epworth Sleepiness Scale [ESS] score >10), areas under the curve were 0.799 (95% confidence interval [CI], 0.777 to 0.822) and 0.833 (95% CI, 0.765 to 0.902). However, both studies oversampled high-risk participants and those with OSA and OSAS. Studies reporting accuracy of PMs for diagnostic testing of persons with suspected OSA found wide ranges for sensitivity and specificity (Type II monitors: 85% to 94% and 77% to 95%; Type III monitors: 49% to 92% and 79% to 95%; Type IV monitors: 7% to 100% and 15% to 100%, respectively, for polysomnography AHI ≥15). Data were limited by imprecision and inconsistency for Type IV monitors. We found sparse data on reliability of PMs.

Our meta-analyses of RCTs found that continuous positive airway pressure (CPAP) effectively reduced AHI to normal or near-normal levels (weighted mean difference [WMD], -33.8 [95% CI, -42.0 to -25.6]; 13 trials; 543 participants), reduced excessive sleepiness as measured by the ESS (WMD, -2.0 [95% CI, -2.6 to -1.4]; 22 trials; 2,721 participants), reduced diurnal systolic blood pressure (WMD, -2.4 [95% CI, -3.9 to -0.9]; 15 trials; 1,190 participants), and reduced diurnal diastolic blood pressure (WMD, -1.3 [95% CI, -2.2 to -0.4]; 15 trials; 1,190 participants) compared with sham. Trial evidence for most health outcomes was too limited to make conclusions (e.g., mortality, cardiovascular events, motor vehicle accidents). However, our meta-analysis for sleep-related quality of life found a significant benefit for CPAP, albeit with a small effect size (Cohen's d, 0.28 [95% CI, 0.14 to 0.42]; 13 trials; 2,325 participants). The effect size was slightly greater among those with excessive sleepiness at baseline but still small (0.33 [95% CI, 0.17 to 0.50]). Mandibular advancement devices (MADs) and weight loss programs also reduced AHI and excessive sleepiness; effect sizes were generally smaller than those for CPAP.

Reporting of harms was suboptimal. Common adverse effects of CPAP included oral or nasal dryness, eye or skin irritation, rash, epistaxis, and pain; common adverse effects of MADs included oral dryness, excess salivation, mucosal erosions, or pain (mucosal, dental, or jaw).

Consistent evidence from prospective cohort studies supports the association between AHI and all-cause mortality; persons with severe OSA die at about twice the rate of controls (pooled hazard ratio [HR], 2.07 [95% CI, 1.48 to 2.91]; 5 studies; 11,003 participants). Risk of cardiovascular mortality was also increased (HRs from 2.9 [95% CI, 1.1 to 7.3] to 5.9 [95% CI, 2.6 to 13.3]).

Limitations: Data on screening accuracy for the MVAP followed by home PM testing were limited by risk of spectrum bias, which may substantially overestimate the accuracy that would be achieved in the general population of asymptomatic adults (or those with unrecognized symptoms). We found no studies that prospectively evaluated screening questionnaires or clinical prediction tools to report calibration or clinical utility for improving health outcomes. Treatment studies did not focus on screen-detected, asymptomatic patients (or those with unrecognized symptoms). Reporting on harms was scant; no studies evaluated overdiagnosis, overtreatment, or psychosocial harms (e.g., anxiety, labeling).

Conclusions: There is uncertainty about the clinical utility of all potential screening tools. Although screening with MVAP followed by home PM testing may have promise for distinguishing persons in the general population who are more or less likely to have OSA, current evidence is limited. Multiple treatments for OSA reduce AHI, ESS, and blood pressure. Although good evidence has established that persons with severe OSA die at twice the rate of controls, trials of CPAP and other treatments have not established whether treatment reduces mortality or improves most other health outcomes, barring evidence of some possible benefit for sleep-related quality of life.

Table of Contents

Figures

Tables

Appendixes

Chapter 1. Introduction

Scope and Purpose

This report will be used by the U.S. Preventive Services Task Force (USPSTF) to inform a recommendation on the topic of screening for obstructive sleep apnea (OSA) in adults. The USPSTF has not previously made a recommendation on sleep apnea. The purpose of this report is to systematically evaluate the current evidence on screening for and treatment of OSA for populations and settings relevant to primary care in the United States. In this report, we summarize the evidence on the benefits and harms of screening for and treatment of OSA and the characteristics of diagnostic tests.

Condition Definition

OSA occurs when airflow is absent or substantially reduced because of upper airway obstruction, but breathing effort persists. It can be categorized as mild, moderate, or severe based on the number of apnea and hypopnea events per hour (**Table 1**). It is different from central apnea, in which both airflow and breathing effort are absent.

OSA severity is usually categorized using the apnea-hypopnea index (AHI) as assessed by a sleep study (polysomnography [PSG]). The AHI incorporates both obstructive and central apnea and hypopnea events, and significantly elevated AHI itself is not synonymous with OSA (because it can indicate OSA, central sleep apnea, or mixed sleep apnea—both OSA and central sleep apnea). The existing literature has used a range of AHI diagnostic thresholds, from 5 to 20[1] episodes per hour for OSA. Both the Centers for Medicare & Medicaid Services and the American Academy of Sleep Medicine define OSA as an AHI or respiratory disturbance index of at least 15 events per hour, or at least 5 events per hour with documented symptoms (e.g., excessive daytime sleepiness, impaired cognition, mood disorders, or insomnia; waking up breath-holding, gasping, or choking; or documented hypertension, ischemic heart disease, or history of stroke).[2,3]

Etiology and Natural History

Persons with OSA have frequent cessation or reduction of airflow during sleep that results in oxygen desaturation and arousals from sleep. Upper airway obstruction during sleep is often associated with anatomical abnormalities or obesity-related peripharyngeal fat that cause narrowing of respiratory passages, decreased pharyngeal muscle tone, and insufficient neuromuscular responses to airway obstruction.[4-6] One longitudinal population-based study of nearly 700 adults (Wisconsin Sleep Cohort Study [WSCS]) found that about 6 percent of 45-year-olds with mild OSA progressed to moderate or severe OSA over 4 years; participants whose body weight increased by at least 10 percent had a 6-fold increased risk of developing moderate or severe OSA.[7] Much variation in development of moderate to severe OSA, however, was not accounted for by weight change. Many adverse clinical outcomes have been associated with

sleep apnea (see Prevalence and Burden below); in particular, untreated, severe OSA (AHI >30) is associated with increased all-cause mortality.[1]

Risk Factors

Risk factors for OSA include male sex (odds ratio [OR], 3.1 [95% (confidence interval) CI, 2.5 to 3.8]),[8] increasing age (40 to 70 years), higher body mass index (BMI), craniofacial and upper airway abnormalities (e.g., children with retrognathia or micrognathia), and postmenopausal status (OR, 3.5 to 4.3 for AHI ≥15).[4,7-22] Persons with OSA (especially moderate to severe OSA) have an increased incidence of hypertension, although the presence of hypertension is not useful in detecting persons at increased risk of OSA.[8] Smoking, alcohol use, sedative use, and nasal congestion have been suspected but have sparse or mixed evidence.[8,23-30]

Prevalence and Burden

Reported estimates of prevalence vary, likely because of the variation in the definitions of OSA used (i.e., different AHI cutoffs), sampling biases, year of publication, or combinations of these factors.[31] A 2013 systematic review estimated a prevalence range of 2 to 14 percent among four community-based studies after correcting for oversampling.[8] The two U.S.-based studies that were included found about 10 percent[15] with mild OSA and 3.8[32] to 6.5[15] percent with moderate or severe OSA when using data from the 1990s. However, prevalence is increasing due to rising rates of obesity.[33,34] Extrapolation of long-term followup data (from 1988–1994 to 2007–2010) from one of the U.S. cohorts estimated a 16 percent prevalence for mild OSA and 10 percent for moderate or severe OSA (AHI ≥15).[33] Evidence about the prevalence of severe OSA (AHI ≥30) is scant, although clearly this prevalence would be lower than the prevalence of combined moderate and severe OSA. The prevalence of severe OSA that would be detected by screening is unknown, including asymptomatic individuals (or individuals with unrecognized symptoms) who are unaware of their diagnosis.

Prevalence appears to increase with age through the sixth to seventh decade and then plateaus.[14,16,17] OSA is approximately 2 to 3 times more common in men than in women, although the gap narrows at the age of menopause in women.[15-17,35] Data published in 2009 (N=1,500) and 2013 (N=1,520) estimated the prevalence around 15 percent in men and 5 percent in women when using either an AHI threshold of 15 or using a combination of AHI of at least 5 with at least one symptom of disturbed sleep.[33,34]

Many adverse clinical outcomes have been associated with sleep apnea. The various adverse outcomes are thought to be primarily due to chronic disturbances in gas exchange (e.g., hypercapnia and hypoxemia), sympathetic nervous system arousal (i.e., oxidative stress caused by intermittent hypoxemia leading to sympathetic activation), and fragmented sleep. Untreated, severe OSA (AHI ≥30) is associated with increased all-cause mortality.[1] However, there is controversy in the literature regarding the extent to which OSA independently contributes to various adverse outcomes beyond the contributions of age, BMI, and other potential confounders. OSA is associated with several cardiovascular risk factors, making it more difficult to establish an independent association between OSA and cardiovascular disease. The adverse

clinical outcomes of untreated OSA that have been reported in various studies include increased risk of motor vehicle and other accidents;[36-42] cognitive impairment;[13,43] lost work days,[44] work disability,[45] and impaired work performance;[46] decreased quality of life;[47] and mortality.[34,39,48,49] In addition, bidirectional associations between OSA and the following have been reported: cardiovascular events,[48,50] coronary heart disease and heart failure,[49,51-55] angina,[56,57] atrial fibrillation,[58] stroke,[49,59] hypertension,[7,12,34,60-63] and diabetes and metabolic syndrome.[64-67] **Appendix A** provides additional details related to prevalence and burden of OSA.

Rationale for Screening

In theory, screening to identify unrecognized OSA followed by appropriate treatment could improve sleep quality and normalize AHI and oxygen saturation levels to prevent adverse health outcomes. Potential screening strategies include formal screening questionnaires and clinical prediction tools that include various combinations of subjective and objective findings. For persons who screen positive, a diagnostic test would be used to determine whether they have OSA—either a formal PSG in a sleep facility or home-based testing with a portable monitor (PM).

Screening Strategies

The available screening questionnaires and clinical prediction tools attempt to identify persons at higher risk of sleep apnea. Many of them combine questions about symptoms with objective findings (e.g., BMI). Screening questionnaires that could be considered for use in primary care include the Epworth Sleepiness Scale (ESS),[68] the STOP Questionnaire (Snoring, Tiredness, Observed Apnea, High Blood Pressure),[69] STOP-Bang Questionnaire (STOP Questionnaire plus BMI, Age, Neck Circumference, and Gender),[70] the Berlin questionnaire,[71] and the Wisconsin Sleep Questionnaire.[15] Previous reviews found that most tools were validated in referral settings (using populations with a higher prevalence of OSA) and not in the general population.[8] Thus, the accuracy and reliability of these tools in general primary care settings were unclear.

The current diagnostic standard for OSA is technologist-attended PSG conducted in a sleep laboratory facility.[72] The use of PSG for diagnosis requires measurement of the following physiologic signals: electroencephalogram, electrooculogram, chin electromyelogram, airflow, oxygen saturation, respiratory effort, and electrocardiogram or heart rate.[73] Additional recommended measurements include body position and leg movements.[73] The frequency of events is typically reported as an AHI.[73] In-laboratory PSG is costly and potentially inconvenient for patients. PMs have been proposed as an alternative.[74] Sleep study monitors are generally classified by the signals recorded[75]: Type I is facility-based PSG; Type II monitors are portable but record the same information as facility-based monitors (perhaps with fewer channels); Type III monitors are portable and have at least two respiratory channels but do not record the channels that differentiate between sleep and wake; and Type IV includes all PMs that fail to meet Type III criteria (**Table 2**).

Treatment Approaches

Continuous positive airway pressure (CPAP) is the standard first-line treatment for OSA.[76] CPAP devices deliver compressed air into the airway, aiming to keep the airway open. The 2013 clinical practice guideline from the American College of Physicians (ACP) recommends 1) that all overweight and obese patients with OSA be encouraged to lose weight (strong recommendation, low-quality evidence), 2) CPAP as initial therapy for patients diagnosed with OSA (strong recommendation, moderate-quality evidence), and 3) mandibular advancement devices (MADs) as an alternative therapy to CPAP for patients with OSA who prefer them or for those with adverse effects associated with CPAP (weak recommendation, low-quality evidence). The ACP concluded that evidence to ascertain the efficacy or comparative efficacy of other therapies that have been studied for OSA was insufficient.[76] These included positional therapy, oropharyngeal exercise, palatal implants, surgical interventions, pharmacologic therapy, and atrial overdrive pacing.

Types of surgical procedures that have been studied or used for OSA include nasal and nasopharyngeal procedures, oral and oropharyngeal procedures, hypopharyngeal and laryngeal procedures, global airway procedures, and upper airway bypass. Specific procedures include uvulopalatopharyngoplasty (UPPP), in which tissue is removed from the throat and the rear of the mouth; maxillomandibular advancement, in which the jaw is surgically moved forward; soft palate implants; nasal polyp removal; tonsillectomy; and tracheostomy. Bariatric surgery for obese patients with OSA has been reported to have positive effects on AHI or sleep-related symptoms.[77-79] Both a 2011 comparative effectiveness review for the Agency for Healthcare Research and Quality (AHRQ)[1] and the related ACP clinical practice guideline[76] concluded that evidence on surgical interventions was insufficient (mainly because each of the seven included studies assessed a different treatment and outcomes were inconsistent).

Published data on the frequency of use of different treatments are limited. The available data suggest that CPAP is by far the most commonly used treatment and that surgical treatments are rarely used.[80,81]

Current Clinical Practice in the United States

Most primary care clinicians do not routinely screen for OSA, and most patients do not discuss their sleep-related symptoms with their primary care clinician; a practice-based research network study of 44 randomly selected practices found that only 20 percent of patients (who regularly visit primary care clinicians) with sleep-related symptoms spontaneously reported their symptoms to their primary care clinician.[82-86] Providers may be unsure about how to identify and diagnose OSA.[83,87-90] There is uncertainty regarding which type of sleep-monitoring devices are best for diagnosing OSA[75] and how to follow patients who have been diagnosed with OSA.

Several guidelines have been issued related to screening, evaluation, and treatment of patients suspected of having OSA (**Appendix A**).

Chapter 2. Methods

Key Questions and Analytic Framework

The Evidence-based Practice Center investigators, USPSTF members, and AHRQ Medical Officers developed the scope and Key Questions (KQs). **Figure 1** shows the analytic framework and KQs that guided the review.

Data Sources and Searches

We searched PubMed/MEDLINE, the Cochrane Library, and EMBASE for English-language articles published through October 25, 2015, with surveillance of the literature through October 5, 2016. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, tests, interventions, outcomes, and study designs. Complete search terms and limits are listed in **Appendix B1**. We conducted targeted searches for unpublished literature by searching ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies that met our inclusion criteria, and added all previously unidentified relevant articles. We reviewed all literature suggested by peer reviewers or public comment respondents and incorporated eligible studies into the final review.

Study Selection

We developed inclusion and exclusion criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs with input from the USPSTF (**Appendix B2**). We included English-language studies of adults age 18 years or older conducted in countries categorized as "very high" on the Human Development Index. We excluded studies of children, adolescents, pregnant women, and adults with acute stroke or other acute conditions that can trigger onset of OSA and studies focused on screening, diagnosis, or treatment of OSA among persons with rare conditions (e.g., acromegaly) for whom testing for OSA would be considered part of management for their disease (rather than screening and primary prevention).

For KQs 1 (direct evidence that screening improves health outcomes) and 2 (accuracy of clinical prediction tools or screening questionnaires), we required studies to enroll asymptomatic adults or persons with unrecognized symptoms of OSA; referral populations were not eligible. For KQ 1, randomized, controlled trials (RCTs) comparing screened with nonscreened groups were eligible. For KQ 2, prospective cohort studies and cross-sectional studies that evaluated screening questionnaires or clinical prediction tools (alone or followed by a home-based PM) compared with overnight PSG conducted in a sleep laboratory were eligible. Studies assessing single patient characteristics or risk factors were not eligible; clinical prediction tools were required to include multiple factors. We excluded studies of persons referred to sleep laboratories because of concern for OSA and excluded studies where only a subgroup (usually the highest

risk group) had PSG because of concern for verification bias.

For KQs 3 (accuracy and reliability of diagnostic tests) and 7 (harms associated with screening and diagnostic tests), referral populations were also eligible (in addition to the populations that were eligible for KQs 1 and 2). For KQ 3, good-quality, recent (within 5 years) systematic reviews comparing PMs (including Type II, III, and IV monitors) with formal, attended PSG conducted in a sleep laboratory (Type I) were eligible for inclusion (**Table 2**). Given that we identified multiple good-quality, recent, and directly relevant systematic reviews for KQ 3, our results for KQ 3 mainly describe previously published systematic reviews. We also included primary studies published after the search cutoff of the most recent systematic reviews (to look for any new studies that might change the findings of previously published systematic reviews). For KQ 7, studies eligible for KQ 1, 2, or 3 that reported false-positive results leading to unnecessary treatment, anxiety, condition-specific distress, or stigma were eligible.

For KQs on benefits (4 and 5) and harms (8) of treatment, RCTs of persons with a confirmed diagnosis of OSA were eligible; studies could include asymptomatic and/or symptomatic adults. We included studies evaluating CPAP, MADs, surgery, and weight loss programs; other treatments were not eligible (e.g., oropharyngeal exercises). For KQ 8, prospective cohort studies with at least 100 participants that reported harms of surgical interventions were also eligible.

For KQ 6 (association between OSA and health outcomes), we included prospective cohort studies that followed participants for at least 1 year and evaluated the association between AHI and health outcomes (by comparing persons with higher vs. lower AHI and following them for incident events). We excluded studies without an attempt to handle potential confounding (e.g., through multivariable analysis and/or restriction), those focused primarily on central sleep apnea, those enrolling patients hospitalized for acute events (e.g., myocardial infarction), and those enrolling patients in a periprocedural period (e.g., ablation for atrial fibrillation). Good-quality, recent (within 5 years), and directly relevant systematic reviews were eligible. However, of the three recent systematic reviews identified,[1,91,92] none met our criteria for direct relevance and good quality; all were rated as fair quality for the information related to KQ 6, and all of them differed from our eligibility criteria (e.g., by combining community-based and referral populations). Therefore, we did not include any previously published systematic reviews for KQ 6.

Two investigators independently reviewed titles and abstracts; those marked for potential inclusion by either reviewer were retrieved for evaluation of the full text. Two investigators independently reviewed the full text to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

Quality Assessment and Data Abstraction

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. A second team member reviewed all data extractions for completeness and accuracy.

We assessed the quality of studies as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B3**).[93] Two independent reviewers assigned quality ratings for each study. Disagreements were resolved by discussion with an experienced team member. We included only studies rated as having good or fair quality.

Data Synthesis and Analysis

We qualitatively synthesized findings for each KQ by summarizing the characteristics and results of included studies in tabular and narrative format. To determine whether meta-analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies following established guidance.[94] We qualitatively assessed the populations, tests, treatments, comparators, outcomes, and study designs, looking for similarities and differences. Eligible outcomes for this review covered a wide range of measures; key measures and questionnaires are summarized in **Appendix B4**.

For KQ 3, when qualitatively evaluating likelihood ratios, we considered positive likelihood ratios (LR+) to indicate a minimal (1–2), small (2–5), moderate (5–10), or large/high (>10) increase in the risk of OSA. We considered negative likelihood ratios (LR-) to indicate a minimal (0.5–1), small (0.2–0.5), moderate (0.1–0.2), or large (<0.1) decrease in the risk of OSA. Likelihood ratios below 0.1 or above 10 are typically thought to provide strong evidence for ruling out (LR- <0.1) or ruling in (LR+ >10) diagnoses.[95,96]

For KQs 4 and 5, when multiple similar studies were available, we used random-effects models using the inverse-variance weighted method (DerSimonian and Laird) to estimate pooled effects.[97] For continuous outcomes (e.g., AHI, blood pressure), we calculated the weighted mean difference (WMD) between intervention and control; when multiple scales were combined in one meta-analysis (for sleep-related quality of life), we used the standardized mean difference (SMD), Cohen's d. For Cohen's d, a small effect size is 0.20, medium effect size is 0.50, and large effect size is 0.80.[98] Whenever possible, we used the number of all randomized patients as the denominator to reflect a true intention-to-treat analysis. For our meta-analyses of CPAP and MAD treatments, we stratified analyses by comparison groups, providing pooled estimates for studies using sham controls (e.g., a sham CPAP device) separately from those not using sham controls. We combined parallel trials and crossover trials but conducted subgroup analyses to explore whether findings differed by this study design feature.

For KQ 6, we conducted meta-analyses of adjusted hazard ratios (HRs) and 95 percent CIs for all-cause mortality (the only outcome for KQ 6 with a sufficient number of similar studies). We used random-effects models to estimate pooled effects. We converted HRs to a log scale and calculated standard errors of log HRs to normalize distributions and stabilize variances. We then used the metan command with the eform command in Stata (StataCorp, College Station, TX) to estimate pooled HRs. We stratified analyses by AHI thresholds corresponding to OSA severity categories. For outcomes other than all-cause mortality, we produced forest plots showing results of individual studies but did not estimate pooled effects because we found too few studies.

For all quantitative syntheses, the chi-squared statistic and the I^2 statistic were calculated to

assess statistical heterogeneity in effects between studies.[99,100] An I^2 from 0 to 40 percent might not be important, 30 to 60 percent may represent moderate heterogeneity, 50 to 90 percent may represent substantial heterogeneity, and 75 percent or greater represents considerable heterogeneity.[101]

We conducted several types of subgroup analyses and sensitivity analyses to explore heterogeneity or robustness of findings. We performed subgroup analyses by OSA severity, baseline sleepiness, and baseline blood pressure.

Quantitative analyses were conducted using Comprehensive Meta-Analysis version 3.3 (Biostat, Inc., Englewood, NJ) and Stata version 14.

Expert Review and Public Comment

A draft report was reviewed by content experts, representatives of federal partners, USPSTF members, and AHRQ Medical Officers and was revised based on comments, as appropriate. It was also posted for public comment.

USPSTF Involvement

This review was funded by AHRQ. AHRQ staff and USPSTF members participated in developing the scope of the work and reviewed draft manuscripts, but the authors are solely responsible for the content.

Chapter 3. Results

Literature Search

We identified 9,841 unique records and assessed 1,443 full texts for eligibility (**Figure 2**). We excluded 1,316 articles for various reasons detailed in **Appendix C** and included 110 studies (published in 127 articles) of good or fair quality. Of the included studies, three were studies of clinical prediction tools or screening questionnaires (KQ 2), 21 were studies of diagnostic test accuracy (KQ 3) (one of which was also included for KQ 2), 76 were RCTs focused on the benefits (KQs 4 and 5) and harms (KQ 8) of treatments for OSA, and 11 provided evidence on the association between AHI and health outcomes (KQ 6). We identified no eligible studies for KQ 1 (direct evidence of screening) or KQ 7 (harms of screening). Details of quality assessments of included studies and studies excluded because of poor quality are provided in **Appendix D**.

Results

KQ 1. Direct Evidence That Screening for OSA Improves Health Outcomes

We found no eligible studies that addressed this question.

KQ 2. Clinical Prediction Tools or Screening Questionnaires

We included three fair-quality studies assessing clinical prediction tools or screening questionnaires compared with facility-based PSG (**Table 3**).[102-104] One evaluated the Berlin Questionnaire[102] and two evaluated the Multivariable Apnea Prediction (MVAP) score, alone and when followed by an in-home PM.[103,104] We found no eligible studies of good or fair quality evaluating other clinical prediction tools or screening questionnaires, such as the ESS, the STOP Questionnaire, or the STOP-Bang Questionnaire.

Two studies that otherwise met our eligibility criteria were excluded because of high risk of bias and therefore rated as poor quality.[69,105] Our main concerns were high risk of selection bias (mainly from attrition bias and spectrum bias, with oversampling of high-risk subjects) and inadequate handling of missing data (**Appendix D**). One of the studies evaluated the STOP and STOP-Bang Questionnaires in a preoperative sample (N=211).[69] The other evaluated the MVAP score alone and when followed by an in-home PM among commercial driver's license holders (N=406).[105]

Berlin Questionnaire

The Berlin Questionnaire classifies risk of OSA as high or low by using three categories related to snoring, tiredness, and blood pressure (at least two positive categories constitutes high risk).[71] Among the 10 questions, it also gathers information on age, sex, height, and weight. The one

included study evaluating the Berlin Questionnaire randomly sampled Norwegians from the National Population Register to complete the Norwegian translation of the Berlin Questionnaire (55% response rate [16,302/29,258]).[102] Of those completing the questionnaire, 24 percent were classified as high risk and 518 had in-hospital PSG. Of those 518, the mean age was 48 years, 45 percent were female, the mean BMI was 28 kg/m^2, and the median AHI was 6.4. Although the group receiving PSG oversampled high-risk participants (70% were high risk), their analyses adjusted for bias in the sampling procedure to report estimated screening properties for the general population. They found suboptimal screening properties (for AHI ≥5: sensitivity of 37.2%, specificity of 84%; for AHI ≥15: 43% and 79.7%, respectively) (**Table 4**). Of note, because it has implications for the validity of studies that oversample high-risk groups (and illustrates the impact of spectrum bias), their unadjusted analyses (reported only in online appendixes) show much better sensitivity but worse specificity (for AHI ≥5: sensitivity of 79.4%, specificity of 40.5%; for AHI ≥15: 82.8% and 34.9%, respectively).

MVAP Score

The MVAP score combines symptoms of snoring, choking, and witnessed apnea events with BMI, age, and sex.[106] It rates apnea risk between zero and 1, with zero representing the lowest risk and 1 representing the highest risk. Both included studies assessing the MVAP were published by the same research group from Philadelphia.[103,104] One study evaluated Medicare recipients (N=452) from the greater metropolitan area, most (74%) of whom had daytime sleepiness.[103] The percentage with OSA was not reported, but 27 percent had OSA syndrome (OSAS) (defined as AHI ≥5 and ESS >10). The other study evaluated patients with hypertension from internal medicine practices at a Veterans Affairs (VA) Medical Center and a university-based hypertension clinic (N=250).[104] Eighty percent of participants had OSA (AHI ≥5); of those, 22 percent had moderate and 25 percent had severe OSA, and 25 percent of all participants had OSAS. Mean ages of participants were 71[103] and 53 years[104], 60 to 64 percent were nonwhite, and mean BMIs were 30 to 32 kg/m^2. The study of Medicare recipients included 70 percent women;[103] the other study included 20 percent women.[104] Key quality limitations included concern for attrition bias[104] and moderate concern for selection bias/spectrum bias (with high prevalence of OSA, OSAS, and/or sleepiness among those receiving PSG)[103,104] (**Appendix D**).

Both studies reported operating characteristics of MVAP to predict *severe* OSAS (AHI ≥30 and ESS >10) using MVAP cutoff scores of 0.48 to 0.49 (**Table 4**). Sensitivity was 90[103] and 91.5 percent,[104] with specificity of 64.4 and 43.9 percent, respectively (95% CIs not reported). The study of Medicare recipients reported reasonable discrimination (area under the curve [AUC], 0.78 [95% CI, 0.71 to 0.85]), whereas the other study found inadequate discrimination (AUC, 0.68 [95% CI, 0.67 to 0.70]). An AUC less than 0.70 is thought to indicate inadequate discrimination.[107,108] Calibration, often assessed by plotting the predicted risk versus the observed rate,[107] was not reported.

The study of patients with hypertension also reported operating characteristics of MVAP to predict *any* OSAS (AHI ≥5 and ESS >10) using an MVAP cutoff score of 0.559. It reported sensitivity of 69.4 percent, specificity of 56.5 percent, and AUC of 0.614.

MVAP Score Followed by an In-Home PM

The same two studies described in the previous section also reported measures of discrimination for the MVAP score followed by an in-home PM (**Table 4**).[103,104] They reported characteristics to predict *severe* OSAS (AHI ≥30 and ESS >10) using different PM-based AHI cutoffs; one used 15[103] and the other used 18.[104] Both studies found better operating characteristics when using MVAP followed by an in-home PM than when using MVAP alone (sensitivity, 88.2% to 90.9%; specificity, 71.6% to 75.7%; AUC, 0.799 to 0.833).

The study of patients with hypertension also reported operating characteristics of MVAP to predict *any* OSAS (AHI ≥5 and ESS >10) using an in-home PM-based AHI cutoff of 13.5. It reported sensitivity of 80.5 percent, specificity of 54.0 percent, and AUC of 0.672.

KQ 3. Accuracy and Reliability of Diagnostic Tests for OSA

We included three studies evaluating Type II PMs (**Appendix E Table 1**), one systematic review and two subsequent studies evaluating Type III PMs (**Appendix E Table 2**), and one systematic review and 14 subsequent studies evaluating Type IV PMs (**Appendix E Tables 3–5**). No studies evaluated the diagnostic accuracy of Type II, III, or IV PMs among subgroups defined by age, sex, or BMI. **Table 5** summarizes the range of sensitivity, specificity, and AUC by type of PM for AHI thresholds of 5, 15, and 30. Additional information on study characteristics and results is available in **Appendix E Tables 1–10**.

Overall, many more studies have evaluated Type III and Type IV monitors than Type II. The best evidence comes from good-quality systematic reviews that reported sensitivity of 93 percent (pooled estimate from in-home studies) and 96 percent (pooled estimate from in-laboratory studies) for Type III PMs and at least 85 percent for Type IV PMs for detecting any OSA (AHI ≥5).[1] Corresponding specificity was 60 percent (in-home) and 76 percent (in-laboratory) for Type III PMs, and ranged from 50 to 100 percent for Type IV PMs.[1] Sensitivity decreased and specificity increased for detecting moderate or greater OSA (AHI ≥15) or severe OSA (AHI ≥30). The ranges of sensitivity and specificity reported across studies for Type IV monitors were wide.

Study participants were generally those referred to sleep units for suspected sleep apnea. We did not find studies that identified participants via screening to identify asymptomatic patients or those with unrecognized symptoms, although detailed reporting of why patients were referred was generally limited. Some studies were conducted in home settings and some tested PMs in laboratory settings; the latter generally reported better accuracy than the former. Reporting of PM AHI cutpoints that were compared with designated PSG AHI cutpoints was limited, with about half of the studies not reporting PM AHI cutpoints. Of those that reported PM AHI cutpoints, the cutpoints used varied across studies, and many studies reported accuracy only for the cutpoints that performed best in their studies.

Type II PMs

We included one study[109] from Spain that evaluated a Type II PM in a sleep laboratory and two

studies[110,111] from Belgium and New Zealand that evaluated Type II PMs in home settings (**Appendix E Table 1**). All 160 participants from the three studies (68, 62, and 30 participants, respectively) had been referred to sleep units for suspected sleep apnea, and in two of the studies,[109,110] more than 80 percent of participants had a PSG AHI of 5 or greater. In one study,[110] patients had to report snoring, excessive daytime sleepiness, or "two other major symptoms of OSA." The other studies did not report information about symptoms or reasons for referral. The mean PSG AHI ranged from 22 to 35 and the mean ESS ranged from 9 to 11. A majority of participants in each of the studies were male and overweight or obese (mean BMI, 29 to 31 kg/m^2).

Diagnostic Accuracy

None of the studies reported the PM AHI cutpoints that were compared with the PSG AHI cutpoints of 5, 15, and 30. To diagnose OSA, defined as a PSG AHI of 5 or greater, Type II PMs had sensitivity of 88 to 96 percent and specificity of 50 to 84 percent. There was a trend of decreasing sensitivity and increasing specificity with increasing PSG AHI cutpoints. Sensitivity was 85 to 94 percent for an AHI of 15 or greater and 64 to 86 percent for an AHI of 30 or greater. Specificity was 77 to 95 percent and 98 to 100 percent for those PSG AHI cutpoints, respectively. In general, Type II PMs were accurate in diagnosing OSA, with AUC values of 85 to 94 across multiple AHI cutpoints. Two thirds of the LR+ and LR- values reported (across multiple cutpoints) indicated a moderate to high increase (LR+) or decrease (LR-) in the risk of OSA in two studies;[109,111] LR+ ranged from 1.8 to 17.6 and LR- ranged from 0.08 to 0.37 across multiple AHI cutpoints.

Reliability

One study[109] compared two expert scorers who manually scored both the PSG and Type II PM; scorers were blind to the patient;s identity and results from the other test (i.e., PSG or PM). The mean PM AHI scores were 19 (scorer 1) and 17 (scorer 2); the kappa (κ) coefficients for PSG AHI cutpoints of 5 or greater, 15 or greater, and 30 or greater were 0.66, 0.70, and 0.85, respectively. Similarly, the mean PSG AHI scores were 22 (scorer 1) and 20 (scorer 2); the κ coefficients for PSG AHI cutpoints of 5 or greater, 15 or greater, and 30 or greater were 0.84, 0.65, and 1.00, respectively. One study[111] evaluated intrascorer reliability by rescoring a random selection of 10 sleep studies; it was not clear which of the 10 sleep studies were in-laboratory PSG or at-home PM. The intrascoring staging concordance was 94 percent and the mean variability in AHI was -0.8.

Type III PMs

We identified one systematic review from 2014[112] and two studies[113,114] that evaluated Type III PMs and were published after the systematic review search cutoff (**Appendix E Table 2**). Both Type III PMs were used at home and included channels for oxygen saturation, airflow, and thoracic and abdominal movements.

Findings of the 2014 Systematic Review

The review[112] covered literature from 2004 through March 2013. Although the overall review included 59 studies (n=5,026 patients), the authors reported meta-analysis results from 19 studies (n=1,507 patients), stratified by setting of PM (i.e., sleep laboratory, home) and AHI cutpoint (i.e., ≥5, ≥10, ≥15, and ≥30).

Patients (n=5,026) with suspected OSA had a mean age of 51 years, a mean ESS score of 12, a mean BMI of 30 kg/m^2, and were predominantly male (ratio of male to female was 2.9 to 1); patient characteristics were not synthesized for the 19 studies in the meta-analysis. The PM performed better in the sleep laboratory setting than at home for all AHI cutpoints. The pooled sensitivity for the home and laboratory settings for an AHI of 15 or greater were 79 and 92 percent, respectively, and generally decreased with increasing OSA severity. The pooled specificity for the home and laboratory settings for an AHI of 15 or greater were 79 and 91 percent, respectively, and generally increased with increasing OSA severity. Discriminatory accuracy of the PMs was high, with AUC for all AHI cutpoints ranging from 85 percent for an AHI of 15 or greater in the home setting to 99 percent for an AHI of 30 or greater in the laboratory setting. Pooled likelihood ratios for the home setting indicated a small to moderate increase (LR+) or decrease (LR-) in the risk of OSA; LR+ ranged from 2.3 to 8.2 and LR- ranged from 0.11 to 0.26 across multiple AHI cutpoints. Seventy-five percent of the pooled likelihood ratios for the laboratory setting indicated a high increase (LR+) or decrease (LR-) in the risk of OSA; LR+ ranged from 3.9 to 14.9 and LR- ranged from 0.03 to 0.09. There was moderate to substantial statistical heterogeneity of results for two AHI cutpoints in the sleep laboratory setting (I^2=85 for AHI ≥5; I^2=66 for AHI ≥15) and for two AHI cutpoints in the home setting (I^2=53 for AHI ≥10; I^2=82 for AHI ≥15); sensitivity analyses, whereby studies with only patients with comorbidities were excluded, did not explain the heterogeneity or substantially change the results.

Description of Type III PM Studies Published After the 2014 Systematic Review Searches

The two included studies (from Spain and Canada) had a total of 184 participants referred to sleep clinics who underwent evaluation for OSA by Type III PMs at home; one study[113] required that participants 1) snored or had some observed apnea events during sleep, 2) had ESS of less than 15, or 3) had a significant comorbidity with daily symptoms (e.g., chronic obstructive pulmonary disease). More than 90 percent of the patients in both studies had a PSG AHI of 5 or greater. The mean PSG AHI in one study[113] was 30 and in the other study[114] ranged from 15 to 25 among patients with low scores and from 35 to 39 among patients with high scores on the Berlin, Sleep Apnea Clinical Score, and STOP-Bang Questionnaires. Patients were more commonly male (55% to 66%) and obese (mean BMI, 30 to 31 kg/m^2); the mean age of patients was 50 to 54 years.

One study did not report the PM AHI cutpoints that were compared with PSG AHI;[114] the other study reported the PM AHI cutpoints that were compared with PSG AHI cutpoints of 5 and 15.[113] To diagnose OSA, defined as a PSG AHI of 5 or greater, Type III PMs had sensitivity of 87 to 96 percent and specificity of 60 to 76 percent. As in the review, sensitivity decreased and specificity generally increased with increasing AHI. AUC values ranged from 82 to 95 percent

across all AHI cutpoints. At a PSG AHI of 15 or greater, one study[113] reported that a PM AHI of less than 7 would exclude OSA and a PM AHI of 22 or greater would confirm OSA. A majority of likelihood ratios indicated a moderate or high increase (LR+) or decrease (LR-) in the risk of OSA (LR+ ranged from 2.6 to 15.50 and LR- ranged from 0.06 to 0.50).

Type IV PMs

We identified one good-quality systematic review from 2011[1] as well as 14 studies[104,115-127] that evaluated the diagnostic accuracy of Type IV PMs and were published after the systematic review search cutoff (**Appendix E Tables 3–5**). Four studies evaluated PMs with 1 channel,[116, 118,121,122] five studies evaluated PMs with 2 channels,[117,120,123,124,126] and five studies evaluated PMs with 3 or more channels.[104,115,119,125,127]

Findings of the 2011 Systematic Review

The good-quality 2011 systematic review[1] covered literature from inception of the databases through September 2010 and summarized findings from the investigators' earlier 2007 technology assessment of PMs[75] that covered literature from inception of the databases through February 2007. The systematic review authors evaluated 24 new studies (seven graded quality A, 11 graded quality B, and six graded quality C) that included 1,865 participants. Seven PMs had more than 3 channels, nine had 2 channels, and nine had a single channel. Patients in 20 of the studies had been referred for suspected sleep apnea or UPPP; the remaining studies included particular populations (e.g., commercial motor vehicle drivers, persons with diabetes, persons with heart failure). The mean ages of patients ranged from 37 to 61 years, and the percentage of male patients ranged from 32 to 100 percent. The mean ESS score ranged from 5.8 to 13.3, and the mean PSG AHI ranged from 14 to 44.

The ranges of sensitivity and specificity for Type IV PMs for the diagnosis of OSA were wide across multiple AHI cutpoints, regardless of the number of channels. Sensitivity ranges were 85 to 100 percent, 43 to 100 percent, and 18 to 100 percent for AHI cutpoints of 5, 15, and 30, respectively. Specificity ranges were 50 to 100 percent, 42 to 100 percent, and 50 to 100 percent for AHI cutpoints of 5, 15, and 30, respectively. The range of sensitivity and specificity increased further when 46 studies (5,008 participants) of Type IV PMs from the 2007 technology assessment were included. Most studies, across both the 2011 systematic review and the 2007 technology assessment, had LR- close to 0.1 for an AHI cutpoint of 5; as AHI cutpoint increased, more studies were at the intersection of an LR+ of 10 or greater or LR- of 0.1 or less, suggesting a better ability to predict elevated AHI.

Description of Studies Published After the 2011 Systematic Review Searches

We included 14 studies of Type IV PMs from Australia or North America (n=4),[104,122,123,127] South America (n=2),[117,124] Europe (n=7),[115,116,118-121,126] and Asia (n=1).[125] Sample sizes ranged from 25[125] to 348[119] participants (total of 1,900 participants) who were primarily referred for suspected sleep apnea. One study referred patients after cardiorespiratory polygraphy,[121] one study referred patients after screening with the Berlin Questionnaire,[127] and one study referred a population of patients with hypertension.[104] Multiple studies required clinical symptoms such as

snoring, excessive daytime sleepiness, or observed apneas during sleep;[117,119,126] one study stated that patients had been referred both with and without symptoms (but did not provide further details).[124] In all but one study,[127] fewer than half of the patients were female. The mean age ranged from 41 to 61 years, and the mean BMI ranged from overweight (26 kg/m^2) to obese (33 kg/m^2). Among the studies reporting ESS scores, the mean ranged from 10 to 12. The mean PSG AHI ranged from 16 to 38, and the percentage of participants with an AHI of 5 or greater was more than 70 percent (among 10 studies reporting).

Eleven studies administered the PMs in the laboratory or hospital setting,[115-118,120,121,123-127] and four studies administered the PMs in the home setting.[104,119,122,127] The single-channel Type IV PMs were pulse oximeters; one study[122] also evaluated a single-channel PM that measured snoring. The 2-channel Type IV PMs were primarily pulse oximeters that also measured snoring,[117,123,124] heart rate,[120,126] and airflow.[124] All of the Type IV PMs with three or more channels included pulse oximeters. Some studies of 2-channel PMs evaluated manual versus automatic scoring,[117] different hypopnea criteria,[117] the use of respiratory disturbance index versus AHI,[124] and different PM AHI cutpoints.[123] Less than half (43%) of studies reported the PM AHI cutpoints that were compared with designated PSG AHI cutpoints.

There was a wide range of sensitivity and specificity for all Type IV PMs across multiple AHI cutpoints (58 to 100 and 35 to 100, respectively); most AUC values were greater than 80. One study of a 4-channel PM reported lower AUC values for a PSG AHI of 5 or greater (AUC, 0.59) when the PM AHI was 8.9, and a PSG AHI of 30 or greater (AUC, 0.73) when the PM AHI was 16.[104] A majority of likelihood ratios indicated a moderate to high increase (LR+) or decrease (LR-) in the risk of OSA; the LR+ ranged from 1.6 (PSG AHI $\geq$10)[119] to 13.7 (PSG respiratory disturbance index $\geq$10),[124] and the LR- ranged from 0.01 (PSG AHI $\geq$5)[104] to 0.57 (PSG AHI $\geq$5).[127]

One study[117] evaluated reliability of a 2-channel PM using a manual scoring method; interrater agreement for the classification of patients with or without OSA was very good (κ=0.81).

KQ 4. Benefits of Treatment for Improving AHI, Sleepiness, and Blood Pressure

We included 76 good- or fair-quality RCTs: 56 trials (described in 60 articles) evaluated CPAP (**Appendix E Tables 11** and **12**),[128-187] 10 trials (12 articles) evaluated MADs (**Appendix E Table 13**),[173,180,188-197] six trials evaluated surgical interventions (**Appendix E Table 14**),[198-203] and six trials (10 articles) evaluated weight loss programs (**Appendix E Table 15**).[204-213]

CPAP

Of the 56 included RCTs, 36 trials (39 articles) compared CPAP with sham CPAP (**Appendix E Table 11**)[128-151,153-157,159-164,166-169] and 20 (21 articles) compared CPAP with other controls (**Appendix E Table 12**).[152,158,165,170-187] Most studies identified participants from sleep clinics or referrals. None of the trials focused on subjects who were screen-detected in primary care settings, but two trials identified participants by screening patients in cardiology or heart failure clinics using the Berlin Questionnaire[178] or the ESS.[184] Most trials were conducted in the United

States (18 trials), United Kingdom (14 trials), or Spain (11 trials); four or fewer were conducted in each of the following: Hong Kong, Australia, Canada, and New Zealand. Duration of treatment ranged from 1 week to 4 years; it was 12 weeks or less in most trials, but five treated participants for 24 weeks or longer,[145,171,172,174,182] including two that followed participants for 52 weeks[171,182] and one that did so for a median of 4 years.[172] Mean age was in the 40s to 50s in most studies and ranged from 42 to 71 years. The vast majority of participants in most trials were men, with 44 trials reporting that less than one third of participants were women. More than half of participants were women in just one trial.[167] More than three fourths of included studies did not report the percentage of minority participants. Of those that did, it ranged from 5 to 56 percent. Mean BMI was 30 to 35 kg/m^2 in most trials (range, 27 to 39 kg/m^2). Mean or median baseline AHI (or similar measure) was in the severe OSA range (AHI ≥30) for more than 75 percent of trials; eight trials reported it in the moderate OSA range,[150,151,155,162,173,178,180,182] and four reported it in the mild OSA range.[166,174,176,183] The range of OSA severity of the enrolled participants in trials most frequently spanned the moderate to severe ranges (29 trials) or the mild to severe ranges (19 trials). Seven trials limited participants to more narrow ranges: mild only,[176] mild to moderate,[151,166,173,183] or severe only.[130,165] One trial did not report sufficient data to determine the range of OSA severity of participants.[174] Mean baseline ESS was 10 or greater in 33 trials, indicating excessive daytime sleepiness. Ten trials reported a mean baseline ESS of less than 10,[130,134,138,147,162,171,172,174,178,181] and 13 trials did not report baseline ESS.

AHI

The trials reporting sufficient data for meta-analysis were all 12 weeks or less. Our meta-analyses found that CPAP reduced AHI more than sham CPAP (WMD, -33.8 [95% CI, -42.0 to -25.6]; 13 trials; 543 participants) and more than other controls (WMD, -25.8 [95% CI, -34.2 to -17.5]; 6 trials; 294 participants) (**Appendix F Figures 1** and **2**). Our meta-analyses found substantial statistical heterogeneity that may be due to variation in CPAP devices (e.g., machines, masks, humidifiers, filters, cushions), participant characteristics (e.g., studies with lower baseline mean AHI finding smaller effect sizes due to ceiling effects), apnea and hypopnea definitions, adherence, study duration, or chance. Nevertheless, all individual studies reported statistically significant improvement, and endpoint AHI values were universally 10 or less for CPAP-treated groups, and most were 5 or less.

ESS

Thirty-four trials reported sufficient ESS data to include in meta-analyses. Most were 12 weeks or less in duration; five followed participants for 24 weeks,[145,174] 48 to 52 weeks,[171,182] or longer.[172] Our meta-analyses found that CPAP reduced ESS more than sham CPAP (WMD, -2.0 [95% CI, -2.6 to -1.4]; 22 trials; 2,721 participants) and more than other controls (WMD, -2.2 [95% CI, -2.8 to -1.6]; 12 trials; 2,488 participants) (**Appendix F Figures 9** and **10**). Our analyses found substantial statistical heterogeneity that may be due to variation in CPAP devices, participant characteristics (e.g., baseline ESS), adherence, study duration, or chance. We were unable to find a clear explanation for the heterogeneity. Among the 27 trials with mean or median baseline ESS of 10 or greater (mean baseline ESS, 12.7) or those that provided subgroup analyses for the participants with excessive sleepiness, our subgroup meta-analyses found a similar result (WMD, -2.4 [95% CI, -2.9 to -1.9]) **(Appendix F Figure 11**). Twenty-three of

those 27 trials reported mean endpoint ESS scores of less than 10 for the CPAP group (mean endpoint ESS <8). Our subgroup meta-analyses by OSA severity (3 categories: mild to moderate OSA, mild to severe OSA, and moderate to severe OSA) did not find a clear difference by OSA severity. Effect sizes were -1.7, -2.1, and -2.4, respectively, and CIs overlapped considerably; the analysis still found considerable statistical heterogeneity within the mild to severe and moderate to severe groups (**Appendix F Figure 12**).

Blood Pressure

Twenty-nine trials reported sufficient blood pressure data to include in meta-analyses. Blood pressure outcomes were reported in a variety of ways (e.g., 24-hour mean arterial blood pressure, 24-hour systolic or diastolic, diurnal mean arterial blood pressures, diurnal systolic). The most common were diurnal systolic and diurnal diastolic blood pressure. Most trials were 12 weeks or less in duration; three followed participants for 24 to 52 weeks.[171,174,182] Our meta-analyses found that CPAP reduced diurnal systolic blood pressure by 2 to 3 points (WMD, -2.4 [95% CI, -3.9 to -0.9]; 15 trials; 1,190 participants; I^2=0%) and reduced diurnal diastolic blood pressure by more than 1 point (WMD, -1.3 [95% CI, -2.2 to -0.4]; 15 trials; 1,190 participants; I^2=16%) compared with sham CPAP. Reduction in 24-hour mean arterial pressure was about 2 points with CPAP compared with sham CPAP (WMD, -2.1 [95% CI, -3.2 to -1.0]; 5 trials; 621 participants; I^2=3%). **Appendix F** provides more detailed results of meta-analyses for all blood pressure measures reported.

Among the six studies that focused on participants with uncontrolled hypertension or that provided subgroup analyses for the participants with uncontrolled hypertension,[135,137,141,162,171,181] our subgroup meta-analyses found similar but slightly larger magnitudes of effect (**Appendix F Figures 34** and **35**). For example, for the three outcomes described in the previous paragraph, we found reductions of -2.5, -2.1, and -2.7, respectively.

Subgroups

None of the included trials reported data by subgroups defined by age, sex, or BMI. We conducted subgroup analyses by OSA severity as described above.

MADs

We included 10 RCTs (described in 12 publications) assessing the effect of MADs on AHI, ESS, or blood pressure (**Appendix E Table 13**).[173,180,188-195,197,214] Six compared MADs with sham devices that did not advance the mandible,[188-192,195] one compared an MAD with a placebo tablet,[173] two compared MADs with no treatment,[197,214] and one compared an MAD with conservative management of OSA with weight loss.[180] All studies recruited participants with known or suspected OSA from specialty clinics, such as sleep medicine or ear, nose, and throat (ENT) clinics. Most studies were conducted in Europe, two were conducted in Australia,[173,192] and one in Hong Kong.[180] Treatment durations ranged from 4 to 12 weeks for most studies, but one study lasted only 1 week[214] and one lasted 24 weeks.[189] Mean age of participants ranged from 45 to 59 years. The vast majority of participants in all trials were men, with women comprising 17 to 25 percent of participants in the nine trials reporting sex. No studies

documented the percentage of minority participants. All studies included participants with mild to moderate OSA, and six studies also included participants with severe OSA.[180,188,191,192,195,214] Mean baseline ESS scores ranged from 11 to 14, indicating excessive daytime sleepiness. One study included only participants with known hypertension.[188]

AHI

Ten trials reported sufficient data for meta-analysis.[173,180,188-192,195,197,214] Our meta-analyses found that MADs improved AHI more than sham (-12.6 [95% CI, -15.5 to -9.7]; 6 trials; 307 participants; I^2=0%) and more than other controls (-8.2 [95% CI, -13.9 to -2.5]; 5 trials; 358 participants; I^2=57%) (**Appendix F Figures 4** and **5**).

ESS

Nine trials reported sufficient data for meta-analysis.[173,180,188,190-192,195,197,214] Our meta-analyses found that MADs improved ESS more than both sham (-1.5 [95% CI, -2.8 to -0.2]; 5 trials; 267 participants; I^2=34%) and other controls (-1.7 [95% CI, -2.2 to -1.2]; 5 trials; 358 participants; I^2=52%) (**Appendix F Figures 13** and **14**).

Blood Pressure

Five trials reported sufficient data for meta-analysis.[180,188,190,191,194] Blood pressure outcomes were reported in a variety of ways (i.e., 24-hour, diurnal or nocturnal, systolic or diastolic). Only one of the trials reported any statistically significant differences between an MAD and sham for some of its blood pressure measures (diurnal systolic blood pressure, -3.0 [95% CI, -5.6 to -0.4]).[194] Our meta-analyses found no statistically significant differences between MADs and comparators for any of the measures (**Appendix F Figures 36–41**).

Subgroups

We found no studies that assessed whether the effect of MADs on intermediate outcomes differs for subgroups defined by age, sex, BMI, or severity of OSA.

Airway Surgery

Five included trials evaluated ENT surgeries (**Appendix E Table 14**). Each trial evaluated a different surgical technique, including radiofrequency surgery of the soft palate,[198] temperature-controlled radiofrequency tissue ablation (TCRFTA),[203] UPPP,[199] laser-assisted uvulopalatoplasty (LAUP),[201] and septoplasty.[202] Three of the trials had sham surgery comparison groups;[198,202,203] two compared surgery with no treatment.[199,201] Sample sizes ranged from 32[198] to 67.[199] Participants were generally identified from ENT clinics, sleep clinics, or referrals. None of the trials focused on subjects who were screen-detected in primary care settings. Trials were conducted in Finland,[198] United States,[203] Sweden,[199] Canada,[201] and Greece.[202] Duration of followup after surgery ranged from 8 weeks[203] to around 15 months.[201] Mean age ranged from 38 to 49 years. The majority of participants were men; four trials included 0 to 24 percent women and the trial of septoplasty included around 40 percent women.[202] None

of the trials reported the percentage of nonwhite participants. Mean BMI ranged from 27 to 32 kg/m^2. Mean AHI was in the severe OSA range (AHI ≥30) for trials of UPPP[199] and septoplasty,[202] in the moderate OSA range for trials of radiofrequency surgery[203] and LAUP,[201] and in the mild range for one trial of soft palate radiofrequency surgery.[198] The full range of OSA severity of participants was moderate to severe in the trial of UPPP,[199] mild to severe in the trial of septoplasty,[202] mild to moderate in trials of radiofrequency surgery[203] and LAUP,[201] and mild only for one trial of soft palate radiofrequency surgery.[198] Mean baseline ESS was 10 or greater in four of the trials, indicating excessive daytime sleepiness; the trial of soft palate radiofrequency surgery reported mean baseline ESS of 8 for one group and 10 for the other.[198]

AHI

All five trials reported AHI. The trials of UPPP[199] and LAUP[201] found greater reductions in AHI for surgery than for no treatment of -26.4 (95% CI, -36.2 to -16.6) and -10.5 (95% CI, -16.9 to -4.1), respectively (**Appendix F Figure 8**). The other three trials (radiofrequency surgery of the soft palate, TCRFTA, or septoplasty) all had sham comparators and found no clinically or statistically significant differences between various airway surgeries and sham.[198,202,203]

ESS

Four of the five trials reported ESS. None of them found a statistically significant difference between participants in surgical and comparator groups (**Appendix F Figure 17**).

Blood Pressure

Only the trial of LAUP (N=46) reported blood pressure outcomes.[201] It reported no significant changes in systolic or diastolic blood pressure in either the LAUP or control group.

Bariatric Surgery

The one included trial randomized 60 morbidly obese (mean BMI, 45 kg/m^2) Australians with moderate to severe OSA (mean AHI around 60) to bariatric surgery or a conventional weight loss program.[200] It followed participants for 2 years. Mean age was close to 50 years. More than 40 percent were female. The trial reported a significant reduction in AHI for both groups; the between-group difference was not statistically significant (-11.5 [95% CI, -28.3 to 5.3]). Similarly, both groups had a significant reduction in ESS, but the between-group difference was not statistically significant (-3.2 [95% CI, -7.2 to 0.8]). The trial found no significant difference between groups for systolic or diastolic blood pressure (mean between-group differences, -1.4 [95% CI, -11.7 to 9] and 2.4 [95% CI, -4.6 to 9.4], respectively).

Weight Loss, Diet, and Exercise Interventions

Six included trials (described in 10 articles) evaluated weight loss programs (**Appendix E Table 15**).[204-213] Each trial evaluated a different intervention and control—two interventions focused primarily on exercise,[204,208] two focused primarily on diet,[207,211] and two used multicomponent lifestyle interventions (exercise, diet, and psychoeducation).[205,210] One compared an inpatient

individualized exercise training with standard health education,[204] one compared exercise training with a stretching control,[208] one compared an intensive lifestyle intervention (consisted of portion-controlled diet, physical activity, and group behavioral weight loss intervention) with a diabetes support and education control,[205] one compared a very low energy diet with usual diet,[207] one compared a very low calorie diet (for 12 weeks) plus supervised lifestyle (for 52 weeks) with usual care (routine lifestyle guidance),[211] and one compared a program of supervised individualized exercise sessions, cognitive-behavioral psychoeducation, and dietary education with advice alone. Sample sizes ranged from 26[204] to 264.[205] Participants were generally identified from sleep clinics, referrals, and advertisements. None of the trials focused on subjects who were screen-detected in primary care settings. Trials were conducted in the United States,[205, 208] Sweden,[207] Finland,[211] United Kingdom,[210] and France.[204] Duration of followup was 4 to 26 weeks for four of the trials; the other two trials followed participants to 4 or 5 years.[205,211] Mean age ranged from 47 to 61 years. Mean BMI ranged from 30 to 40 kg/m^2. Mean AHI was in the moderate to severe OSA range for four of the trials, in the mild range for the trial that evaluated very low calorie diet plus supervised lifestyle,[211] and in the moderate to severe range but controlled with CPAP use in one trial.[210] Mean baseline ESS was 10 or greater in two trials,[204,211] less than 10 in three,[207,208,210] and not reported in one.[205] The weight loss achieved by intervention groups was very limited in one trial (-0.3 kg)[208] and modest in another (-2.3 kg)[210] but reached more clinically significant levels in the rest (5- to 20-kg reduction).[205,207,213]

AHI

Five trials reported AHI.[204,205,207,208,213] Four of the five found statistically significant reductions in AHI, ranging from -5.8 (95% CI, -9.7 to -1.9) to -23 (95% CI, -30.1 to -15.9) (**Appendix F Figure 6**). The trial reporting the largest reduction in AHI (a reduction nearing that achieved by CPAP) also reported a much larger weight reduction than other trials (-20 kg over 9 weeks from a very low energy diet).[207] Our meta-analysis found a WMD of -12.4 (95% CI, -19.4 to -5.5). We found substantial statistical heterogeneity (I^2=79%), which was no longer present after removing the one study with much larger weight reduction (and the largest reduction in AHI) (**Appendix F Figure 7**).

ESS

Four trials reported ESS.[204,207,208,213] Three of the four found statistically significant reductions in ESS, ranging from -3 to -7. Our meta-analysis found that weight loss interventions improved ESS more than controls (-3.4 [95% CI, -5.9 to -1.0]; 4 trials; 213 participants; I^2=78%) (**Appendix F Figure 15**). The substantial statistical heterogeneity was reduced when removing the one trial that enrolled participants with mild OSA (**Appendix F Figure 16**).

Blood Pressure

Three trials reported blood pressure outcomes.[209-211] One found similar blood pressure reductions for exercise training (N=27) and a stretching control (N=16) after 12 weeks, although it reported a slightly greater magnitude of reduction for the stretching control group (systolic blood pressure, -6.7 vs. -7.3; diastolic blood pressure, 0 vs. -2.7; between-group difference, 95% CI, or p-value not reported).[209] Another trial (N=60) found no significant difference between a

multicomponent lifestyle intervention and advice only at 13 weeks (mean difference, 0 [95% CI, -5 to 4]) or after another 13 weeks off treatment (mean difference, -2 [95% CI, -7 to 4]).[210] The other trial (N=81) reported no significant difference between a very low calorie diet with supervised lifestyle counseling and a routine lifestyle counseling control group at 12 months (-1.7 vs. -1.1; p=0.88; and -1.9 vs. -0.4; p=0.62) or at 2-year postintervention followup.[211,212]

Subgroups

We found no studies that assessed whether the effect of weight loss interventions on intermediate outcomes differs for subgroups defined by age, sex, BMI, or severity of OSA.

KQ 5. Benefits of Treatment for Improving Health Outcomes

We included 50 good- or fair-quality RCTs that reported at least one eligible health outcome (47 of these were included in KQ 4). Most of those were short-term RCTs (≤12 weeks) that reported zero or few deaths over the course of the study. The characteristics of these studies are summarized in **Appendix E Tables 13**–**16**, and the results are summarized in **Appendix E Tables 17**–**19**.

CPAP

Thirty-five RCTs comparing CPAP with sham CPAP[128,130,137-139,142,145,147,150,151,154,155,157,161-164,166,168,172,215] or another control[170,172-178,180,182-184,216,217] reported at least one eligible health outcome. Most trials identified participants from sleep clinics or referrals, and none focused on persons who were screen-detected in primary care settings. Ten trials were conducted in the United States;[139,145,147,150,155,157,166,178,183,215] others were set in Canada,[184] Australia,[140,161,173] New Zealand,[151] Hong Kong,[180] United Kingdom,[142,162-164,168,174-177,182,216,217] and Spain.[128,130,137,138,154,170,172] Most trials followed participants for 12 weeks or less; four trials measured outcomes over 24 weeks or longer,[145,172,174,182] including one that followed participants for a median of 4 years.[172] Most trials enrolled populations with a mean age in the 40s to 50s (range, 42 to 71 years). The vast majority of participants in most trials were men; women made up a third or less of the enrolled population in 26 trials. All eight trials that described race enrolled a majority of white participants. Mean BMI was 30 to 35 kg/m^2 in most trials (range, 27 to 37 kg/m^2). Mean or median baseline AHI (or similar measure) was in the severe OSA range (AHI ≥30) for more than half of trials; nine trials reported it in the moderate OSA range,[150,151,155,162,173,178,180,182,216] and five reported it in the mild OSA range.[166,174,176,183,217] The range of OSA severity of enrolled participants in trials most frequently spanned the moderate to severe range (27 trials) or the mild to severe range (15 trials). Six trials limited participants to more narrow ranges: mild only,[176] mild to moderate,[151,166,173,183] or severe only.[130] One trial did not report sufficient data to determine the range of OSA severity of participants.[174] Mean or median baseline ESS was 10 or greater in most trials (23), indicating excessive daytime sleepiness. Five trials reported a mean baseline ESS of less than 10,[130,138,162,172,174] and seven trials did not report baseline ESS.

Mortality

Thirty-one RCTs reported on mortality (**Appendix E Table 17**). The vast majority (29 RCTs)

reported mortality rates at 12 weeks or less, and the vast majority (27 RCTs; 2,211 total participants) reported no deaths in any study group;[128,130,137,139,140,142,147,150,151,154,155,157,162-164,166,170,173,175-178,180,183,184,216,217] two trials (462 total participants) reported one death, either in the CPAP[174] or sham CPAP group at 12 weeks.[138] Two RCTs assessed mortality over a longer duration.[145,172] One (N=1,105) reported two deaths in each study arm over 24 weeks.[145] The other (N=723) reported eight deaths in the CPAP group and three in the control group over about 4 years (incidence density ratio, 2.6 [95% CI, 0.70 to 11.8]; p=0.16).[172]

Quality of Life

Twenty-two RCTs reported quality-of-life measures (**Appendix E Table 17**). Fourteen measured quality of life using the Medical Outcome Short-Form (36-Item) Health Survey (SF-36).[130,138,142,151,154,163,164,166,173,174,176,180,182,183] Only one RCT (N=179) reported changes in total SF-36 scores; at 12 weeks, participants randomized to CPAP showed greater improvement than controls in the total SF-36 score (mean change from baseline, 4.7 vs. 2.0; p<0.05).[173] Most studies using the SF-36 reported changes separately for the physical component score (PCS) and the mental component score (MCS). Some studies only reported data for all or some of the eight subscales of the SF-36. Eight trials reported sufficient data for meta-analysis of SF-36 MCS.[130,138,142,154,163,164,166,174] Seven of these compared CPAP with sham CPAP and reported outcomes at 12 weeks or less; one trial compared CPAP with another control and reported outcomes at 24 weeks.[174] Our meta-analysis found no difference between CPAP and comparators in the change from baseline SF-36 MCS (WMD, 1.2 [95% CI, -0.8 to 3.2]; 8 trials; 1,039 participants) (**Appendix F Figure 42**). Seven trials reported sufficient data for meta-analysis of SF-36 PCS;[130,138,142,154,163, 164,166] all compared CPAP with sham and reported outcomes at 12 weeks or less. Our meta-analysis found that CPAP improved scores significantly more than sham (WMD, 2.3 [95% CI, 0.2 to 4.4]; 7 trials; 648 participants) (**Appendix F Figure 43**). Both meta-analyses found moderate statistical heterogeneity.

Seven RCTs measured general quality of life using another measure (**Appendix E Table 17**). Two RCTs measured changes in quality of life using the EuroQol.[137,174] In one trial (N=323), there was no difference between CPAP and control groups in the change from baseline total score at 24 weeks.[174] The other trial (N=340) only reported within-group changes; the CPAP group improved at 12 weeks (p<0.001 compared with baseline; effect size [standard deviation units] 0.38), but no improvement was seen in the control group.[137] Five RCTs assessed quality of life using the Nottingham Health Profile. Three of them found no difference between groups in the change from baseline overall scores,[175,176,217] one reported greater improvement in the CPAP group compared with controls (4.9 vs. 7.9 [lower scores indicate greater improvement]; p=0.002),[216] and one reported only outcomes for six subscore domains (greater improvement for CPAP than control on two of six scores) (**Appendix E Table 17**).[170]

Thirteen RCTs assessed sleep-related quality of life—six using the Sleep Apnea Quality of Life Index (SAQLI)[164,168,174,180,182,218] and seven using the Functional Outcomes of Sleep Questionnaire (FOSQ).[130,151,154,161,166,173,177] Most trials reported outcomes at 12 weeks or less; two reported outcomes at 24 weeks (or 6 months)[174,218] and one at 52 weeks.[182] Eight trials compared CPAP with sham,[130,151,154,161,164,166,168,218] and the others compared CPAP with another control.[173,174,177,180,182] Our meta-analysis (combining SAQLI and FOSQ scores) found that

CPAP was associated with improved sleep-related quality-of-life scores compared with controls (SMD, 0.28 [95% CI, 0.14 to 0.42]; 13 trials; 2,325 participants) (**Appendix F Figure 44**). Our sensitivity analysis including only studies with mean baseline ESS of 10 or greater found a slightly greater but similar effect size (0.33 [95% CI, 0.17 to 0.50]; 9 trials; 1,709 participants) (**Appendix F Figure 46**).

Cognitive Impairment

Twelve RCTs reported one or more measures of cognitive function.[130,145,147,151,170,173,175,176,182,215-217] In general, studies assessed cognitive function using heterogeneous outcome measures and reported inconsistent results (**Appendix E Table 17**).

Motor Vehicle Accidents

Three RCTs reported on the incidence of motor vehicle accidents. In one trial (N=212), there were no accidents in either group at 12 weeks.[178] The other two reported similar rates between CPAP and comparator groups over 24 weeks (10 vs. 11 accidents out of 1,105 participants)[145] or over 1 year (2 vs. 1 accidents out of 278 participants).[182]

Cardiovascular Events

Eight RCTs reported on the incidence of one or more cardiovascular events.[138,145,151,168,172,174,178,182] Five (1,529 total participants) reported on the incidence of myocardial infarction; a total of one myocardial infarction occurred (combined) in either group (the control group) across four of the trials over 3 weeks to 1 year.[151,174,178,182] The trial with the longest duration (723 participants) reported two myocardial infarctions in the CPAP group and eight in the control group over 4 years.[172]

Four RCTs reported on the incidence of angina[138,174,182] or unstable angina;[178] trial durations were 52 weeks,[182] 24 weeks,[174] and 12 weeks.[138,178] Overall, too few events occurred to draw conclusions (CPAP vs. comparators: total of 4 vs. 9 angina events among a total of 570 participants).[138,174,178,182]

Three RCTs reported on the incidence of atrial fibrillation; trial durations were 12 weeks,[178] 24 weeks,[174] and 1 year.[182] In the trial measuring outcomes at 12 weeks, one participant developed atrial fibrillation (randomized to the control group);[178] in the trials assessing outcomes at 6 months and 1 year (669 total participants), there was no difference in the incidence of atrial fibrillation between groups (12 vs. 19 events).[182]

One RCT reported one event in either group for each of the following (details are provided in **Appendix E Table 17**): unspecified tachyarrhythmia requiring hospitalization,[178] percutaneous coronary intervention for worsening angina,[178] and emergent cardiac surgery.[168] One trial reported only an overall number of cardiovascular events (as adverse events) without describing how outcomes were measured or defined (31 vs. 29 events in CPAP and control arms, respectively).[145] One trial reported hospitalizations for unstable angina or arrhythmia (17 vs. 11 in CPAP and control arms, respectively, out of 723 participants).[172]

Cerebrovascular Events

Four included RCTs (1,604 total participants) reported on the incidence of transient ischemic attacks[172,174,182] and/or strokes.[172,174,178,182] Trial durations were 12 weeks,[178] 24 weeks,[174] 1 year,[182] and 4 years (median followup).[172] Overall, too few events were observed to draw conclusions (CPAP vs. comparators: total of 4 vs. 7 transient ischemic attacks and 3 vs. 3 strokes, combining all trials). The trial with the longest followup (723 participants with median followup of 4 years) reported the most observed events, reporting fewer transient ischemic attacks in the CPAP group than in the control group (2 vs. 5) but more nonfatal strokes (3 vs. 2).[172]

Heart Failure

In one RCT (N=723), three participants in the CPAP group developed new heart failure compared with five in the control group over a median followup of 4 years.[172]

Headaches

In one RCT (N=37), three participants in the control group developed headaches at 4 weeks compared with none in the CPAP group.[176]

Subgroups

The APPLES (Apnea Positive Pressure Long-term Efficacy Study) trial found no significant overall difference between CPAP and sham CPAP for improvement in quality of life after 6 months.[218] However, subgroup analyses stratified by OSA severity found that greater improvement in quality of life may occur for persons with severe OSA treated with CPAP who used it more than 4 hours per night (compared with those treated with sham CPAP; between-group difference on SAQLI, 0.2; $p<0.05$).[218] We found no other studies that reported difference for the effect of CPAP on health outcomes for subgroups defined by age, sex, BMI, or severity of OSA.

MADs

We included six RCTs assessing the effect of MADs on health outcomes, including mortality, quality of life, cognitive impairment, and cardiovascular events (**Appendix E Table 13**).[173,180,189,191,197,214] None of the included studies reported the incidence of cerebrovascular events, heart failure, or headaches. Two studies compared MADs with sham devices that did not advance the mandible,[189,191] one compared an MAD with a placebo tablet,[173] two compared MADs with no treatment,[197,214] and one compared an MAD with conservative management of OSA with weight loss.[180] All studies recruited participants with known or suspected OSA from specialty clinics, such as sleep medicine or otolaryngology. Four studies were conducted in Europe, one in Australia,[173] and one in Hong Kong.[180] Treatment durations ranged from 4 to 12 weeks for most studies, while one lasted for only 1 week[214] and one for 24 weeks.[189] Mean age of participants ranged from 45 to 51 years in all studies. The vast majority of participants were men, with women comprising 18 to 27 percent in the five trials reporting sex. No studies reported

percentage of minority participants. All studies included participants with mild to moderate OSA, and three also included participants with severe OSA.[180,191,214]

Mortality

Among the four trials that reported on mortality over 1 to 12 weeks,[173,191,197,214] three of the trials reported no deaths in any participants. The other trial reported one death in the group that received no treatment.[191]

Quality of Life

Five included trials reported at least one quality-of-life measure.[173,180,189,191,197] All five used the SF-36, two also used the SAQLI,[180,197] and two also used the FOSQ.[173,197] Because of heterogeneity in the reporting of SF-36 outcomes, the results were not amenable to meta-analysis. Overall, results were mixed, with some studies finding no significant benefits of MADs for improving quality of life,[180,189] some reporting possible benefits for some measures or subscales but not others,[173,191] and some reporting benefits for some overall quality-of-life scores.[197] Further details and specific data are provided in **Appendix E**. Because of inconsistency, imprecision, and heterogeneity of reporting, findings are insufficient to make conclusions about the potential benefits of MADs for improving quality of life.

SF-36

The trial (N=39) that compared an MAD with a sham device for 24 weeks found no significant differences in multiple SF-36 subscores.[189] A four-arm crossover trial (N=90) of three different types of MADs compared with no treatment found significant improvement in the SF-36 PCS for a SleepPro2 (MEDiTAS, Milton Keynes, UK) MAD only, and the SF-36 MCS for a custom MAD only.[197] A trial (N=67) that compared an MAD with conservative management found no significant difference in SF-36 Physical Function, Mental Health, and General Health subscores.[180] Another trial (N=93) that compared an MAD with a sham device or no treatment found no significant benefit for SF-36 PCS but reported some improvement for SF-36 MCS scores (although it was unclear if the improvement was significantly greater than that with controls because of how the findings were reported).[191] A trial (N=197) that compared 12 weeks of an MAD with placebo tablet found a significant improvement in overall SF-36 score from baseline but not compared with placebo tablet.[173]

Disease-Specific Quality-of-Life Measures

The trial that compared an MAD with conservative management for 10 weeks found significant improvements in Emotional and Symptoms subscores but not in total SAQLI score.[180] The four-arm crossover trial that compared three types of MADs (each for 6 weeks) found significant improvement in total SAQLI score for all devices and nearly all subscores for all devices.[197] The trial that compared an MAD with a placebo tablet reported significant improvement in mean FOSQ score at 12 weeks but not in subscores other than Social Outcomes.[173]

Other Health Outcomes

We included one trial assessing each of the following outcomes for participants using MADs over 6 to 12 weeks: cognitive impairment,[173] motor vehicle accidents,[197] and cardiovascular events.[197] Specific data are provided in **Appendix E**. Because of unknown consistency, imprecision, and very limited numbers of events, findings are insufficient to make conclusions about the potential benefits of MADs for these outcomes.

Subgroups

We found no studies that assessed whether the effect of MADs on health outcomes differs for subgroups defined by age, sex, BMI, or severity of OSA.

Airway Surgery

Four of the five included RCTs evaluating ENT surgeries described in KQ 4 reported at least one included health outcome (**Appendix E Table 18**).[198,201-203] Each trial evaluated a different surgical technique, including radiofrequency surgery of the soft palate,[198] TCRFTA,[203] LAUP,[201] and septoplasty.[202] These studies are described in detail in KQ 4.

Mortality

Three RCTs reported no deaths in any study arms over 12 weeks to around 15 months.[198,201,202]

Quality of Life

Three RCTs reported quality-of-life measures (**Appendix E Table 18**). Two trials (92 participants combining both trials) measured general quality of life using the SF-36; there were no differences between groups in change from baseline for PCS or MCS over 8 to 24 weeks.[198, 203] Two trials measured sleep-related quality of life.[201,203] The trial (N=46) comparing LAUP with no treatment found no significant difference between groups for overall SAQLI scores but reported a difference for the SAQLI Symptoms subscore.[201] The trial (N=60) comparing TCRFTA with sham surgery reported greater improvement in overall FOSQ scores for the TCRFTA group (between-group difference, 0.9 [95% CI, -0.1 to 1.9]; one-sided p=0.04) but no difference on the Symptoms of Nocturnal Obstruction and Related Events score.[203]

Cognitive Impairment

One RCT (N=60) comparing TCRFTA with sham surgery found no difference between groups in three measures of reaction times measured using the Psychomotor Vigilance Task (slowest reaction time, median reaction time, and fastest reaction time).[203]

Subgroups

We found no studies that assessed whether the effect of airway surgery on health outcomes differs for subgroups defined by age, sex, BMI, or severity of OSA.

Bariatric Surgery

One RCT (N=60) compared bariatric surgery with a conventional weight loss program in persons with severe OSA (mean AHI ranged from 57 to 65 across study arms);[200] characteristics are described in KQ 4 and **Appendix E Table 18**. There were no deaths in either group at 2 years. At 2 years, participants randomized to bariatric surgery had greater improvement in quality of life measured by the SF-36 PCS (between-group difference, 9.3 [95% CI, 0.5 to 18.0]; p=0.04); however, there was no difference between groups in the change from baseline SF-36 MCS (between-group difference, -0.3 [95% CI, -5.3 to 4.8]; p=0.92).[200] One person in the bariatric surgery arm developed headaches during the study compared with no participants in the conventional weight loss group.[200]

Weight Loss Programs

Six RCTs (described in nine articles) evaluated weight loss programs; the characteristics are described in detail in KQ 4 and **Appendix E Table 18**.[204-213]

Mortality

Four RCTs (45 participants combining all studies) assessed mortality; three reported no deaths in any group over 9 to 208 weeks,[205,207,208] and one reported one death at 52 weeks (it was not reported which study arm the person was in).[211]

Quality of Life

Four RCTs assessed quality of life.[204,208,210,211] Two measured general quality of life using the SF-36;[204,208] both reported on scores across the eight domains but did not report a PCS, MCS, or overall score (detailed results are in **Appendix E Table 18**). In one trial comparing an inpatient weight loss program with a control, the authors only provide within-group changes from baseline; the control group did not improve in any of the eight SF-36 domain scores, while the weight loss program group improved significantly on most domain scores (except for vitality and emotional role limitation).[204] The trial of very low calorie diet plus supervised lifestyle compared with usual care found no difference between groups in the mean change from baseline 15-dimensional measure of health-related quality-of-life scores at 52 weeks (mean change from baseline score, 0.041 vs. 0.022; p=0.167).[211] One RCT measured changes in sleep-related quality of life using the FOSQ; there was no difference between groups in change from baseline scores (p-value was not significant, per authors).[208] Finally, the RCT that compared a multicomponent lifestyle intervention with advice only for obese long-term CPAP users found no difference on the EuroQol EQ-5D-3L Visual Analogue Scale between groups at the end of the 13-week treatment phase (between-group mean difference, 3 [95% CI, -4 to 10]), but it reported greater improvement for the intervention group 13 weeks after the treatment phase ended (between-group mean difference, 9 [95% CI, 2 to 16]).[210]

Cognitive Impairment

One trial comparing exercise training with a stretching control assessed for changes in cognitive

function over 12 weeks with the Psychomotor Vigilance Test, Stroop Color-Word Test, and Trail-Making Test; there were no difference between groups on any of these measures.[208]

KQ 6. Association Between OSA and Health Outcomes

We included 11 fair- or good-quality prospective cohort studies (described in 12 articles) that assessed the association between AHI and health outcomes (**Appendix E Table 20**).[50,219-229] All focused on community-based participants; one also enrolled some participants from a sleep clinic.[50] Three good-quality studies analyzed participants from the Sleep Heart Health Study (SHHS),[224,225,227] a cohort of men and women age 40 years or older recruited from other prospective cohort studies (e.g., Framingham Offspring and Omni Study, Atherosclerosis Risk in Communities Study) between 1995 and 1998. Two included studies evaluated the WSCS,[221,226] a community-based, random sample of state-employed adults ages 30 to 60 years. Two articles reported data from the same study (Busselton Health Study) for different durations of followup.[228,229]

Six studies (described in seven articles) reported the association with all-cause mortality;[220,221, 223,226-229] three with cardiovascular mortality;[50,226,227] two with cardiovascular events;[50,224] and one each with cancer-related mortality,[221] stroke,[225] cognitive decline,[219] and cognitive impairment or dementia.[222] We found no eligible studies reporting on the association between AHI and quality of life, motor vehicle accidents, or headaches. Two studies that evaluated the association between AHI and stroke[230,231] and one that evaluated the association between AHI and cognitive function were excluded because of poor quality (**Appendix D Table 11**).[232]

Nine of 11 studies were conducted in the United States, one was conducted in Spain,[50] and one was conducted in Australia.[228] Most studies followed patients for 8 to 14 years; followup ranged from a mean of 3.4[220] to 22 years.[221] Three studies included only men; half of the studies included between 45 and 56 percent women. Two studies did not report the proportion of nonwhite participants;[50,228] other studies reported a range from 5 to 26 percent. Mean BMI ranged from 26 to 30 kg/m^2 in most studies. Most studies did not report mean AHI or mean ESS at baseline. The percentage of participants with diabetes ranged from 3 to 13 percent among studies reporting it.

Participants were generally untreated for OSA or analyses excluded those who were treated. Eight of the 11 studies reported either excluding persons who received treatment from the study or running additional analyses that excluded those who were treated; the percentage of participants who were treated was low, ranging from 0 to 9.9 percent. Two of the smallest included studies (total sample sizes of 393[229] and 289[223]) did not report the percentage who were treated for OSA but reasoned that any potential treatment would only have resulted in their data underestimating the true HR. One study reporting the association between AHI and stroke included 1.9 percent (102/5,422) who were treated with CPAP during the study and did not report sensitivity analyses that excluded those participants.[225]

All-Cause Mortality

Six studies (described in seven articles) evaluated AHI as a predictor of all-cause mortality.[220,221,

[223,226-229] These included two studies reporting on WSCS participants[221,226] and two articles (one study) reporting on different lengths of followup for the Busselton Health Study.[228,229] Sample sizes ranged from 289[223] to 6,294.[227] Mean duration of followup ranged from 3.4[220] to 20 years.[229] Mean age ranged from 48[226] to 78 years.[223]

In multivariate analyses, all included studies reported that persons with severe or moderate to severe OSA at baseline had a higher risk of death. HRs ranged from 1.46[227] to 6.24.[228] Variables included in the models are detailed in **Appendix E Table 21**. Briefly, all included age and some medical conditions in the final model; all considered BMI (although it did not remain in the final model in one study); most included smoking, sex, race, hypertension or blood pressure, and diabetes. Our meta-analysis of five studies (using one of the two publications from the WSCS to avoid double-counting and using the article reporting longer followup for the Busselton Health Study) found that persons with severe or moderate to severe OSA died at about twice the rate of controls (**Figure 3**) (HR, 2.07 [95% CI, 1.48 to 2.91]). The analysis found moderate statistical heterogeneity (I^2=58%), likely due to variation in AHI thresholds for the study groups (e.g., using 15, 20, or 30 to define the highest risk group), duration of followup, and approach to analyses (i.e., variables included in multivariate models).

Two studies using data from the SHHS[227] or the WSCS[226] assessed whether moderate (AHI, 15 to <30) or mild (AHI, 5 to <15) OSA is associated with mortality. Neither of the individual studies nor our pooled analyses found a statistically significant association between moderate or mild OSA and all-cause mortality (**Figure 3**).

Two of the included studies reported evidence for subgroups—either by sex and age[227] or by presence of sleepiness.[223] The former used the SHHS data (N=6,294) and reported that the association between an AHI of 30 or greater and mortality was only statistically significant for men age 70 years or younger (adjusted HR, 2.09 [95% CI, 1.31 to 3.33]) but not for men older than age 70 years (HR, 1.27 [95% CI, 0.86 to 1.86]) or for women of any age (HR, 1.40 [95% CI, 0.89 to 2.22]).[227] The latter found that the association between an AHI of 20 or greater and death was limited to those with excessive daytime sleepiness (determined by self-report of having a problem with feeling sleepy or struggling to stay awake during the daytime ≥3 or ≥4 times a week) but was not significant for those without excessive daytime sleepiness (HR, 2.28 [95% CI, 1.46 to 3.57] vs. 0.74 [95% CI, 0.39 to 1.38]) compared with a reference group with an AHI of less than 20 and no excessive daytime sleepiness.

Cardiovascular Mortality

Three studies evaluated the association between AHI and cardiovascular mortality.[50,226,227] Sample sizes ranged from 1,522[226] to 6,294.[227] Mean duration of followup ranged from 8.2[227] to 13.8 years.[226] Mean age ranged from 48[226] to 63 years.[227]

In multivariate analyses, all three studies reported that persons with severe or moderate to severe OSA at baseline had a higher risk of death (**Figure 4**). We did not pool data from these three studies because of substantial heterogeneity; the SHHS only reported data for men and used different AHI thresholds than the other two studies (combining moderate and severe OSA vs. reporting data for severe OSA separately). It reported the smallest association (men only: HR,

1.69 [95% CI, 1.13 to 2.52]) and noted that an association between moderate to severe OSA and cardiovascular mortality was not identified for women.[227] For the other two studies, HRs ranged from 2.9 to 5.9. The strongest association was reported by the WSCS (HR, 5.9 [95% CI, 2.6 to 13.3]; when excluding those treated with CPAP: HR, 5.2 [95% CI, 1.4 to 19.2]).[226] Variables included in the models are detailed in **Appendix E Table 21**. Briefly, all included age, BMI, smoking, and multiple medical conditions or used matching for age and BMI. Two of three included alcohol use, blood pressure, and cholesterol.

Cancer-Related Mortality

One publication used a 22-year followup of the WSCS cohort (N=1,522) to evaluate the association between AHI and cancer-related mortality.[221] Participants had a mean age of 48 years, 45 percent were female, and mean BMI was 30 kg/m^2. Fifty participants had cancer-related deaths (eight from lung cancer; four each from colorectal, ovarian, and endometrial cancer; three each from brain, breast, and bladder cancer; and multiple other cancers causing one or two deaths each). The study reported a significant association between an AHI of 30 or greater and cancer-related mortality (HR, 4.8 [95% CI, 1.7 to 13.2]), and results suggested a dose-response association between AHI and cancer-related mortality (**Appendix E Table 21**) (HR for mild OSA, 1.1 [95% CI, 0.5 to 2.7]; HR for moderate OSA, 2.0 [95% CI, 0.7 to 5.5]). The model included adjustment for age, sex, BMI, and smoking; additional adjustment for alcohol use, physical activity, educational status, diabetes, waist circumference, and sleep duration did not materially change results (data not reported). Similarly, analyses stratified for sleepiness and obesity found no clinically important differences. Analyses removing those treated with CPAP resulted in slightly increased HRs (data not reported).

Cardiovascular Events

Two studies following patients for approximately 8 to 10 years evaluated the association between AHI and cardiovascular events (**Appendix E Table 20**).[50,224] Sample sizes were 1,651[50] and 4,422.[224] One was conducted in Spain; one was conducted in the United States and reported on participants from the SHHS.[224] Mean ages of participants were 50[50] and 63 years.[224] One evaluated men only;[50] slightly more than half were women in the other.[224]

The two studies reported different outcomes. The Spanish study reported 144 total nonfatal cardiovascular events (including nonfatal myocardial infarction, nonfatal stroke, coronary bypass surgery, and percutaneous transluminal coronary angiography).[50] In multivariate analyses, those with untreated severe OSA at baseline had a higher risk of events (OR, 3.17 [95% CI, 1.12 to 7.52]), adjusted for age; hypertension; presence of cardiovascular disease (ischemic heart disease, congestive heart disease, or cerebrovascular disease); diabetes; lipid disorders; smoking status; alcohol use; systolic and diastolic blood pressure; blood glucose; total cholesterol; triglycerides; and current use of antihypertensive, lipid-lowering, and antidiabetic drugs; they also matched for age and BMI.

The SHHS study reported 473 total incident coronary heart disease events (composite of first occurrence of myocardial infarction, coronary heart disease deaths, and revascularization procedures) and 308 total incident heart failure events.[224] Neither incident coronary heart disease

nor incident heart failure were associated with OSA (of any severity) for men or women when adjusting for age, race, BMI, smoking, total and high-density lipoprotein cholesterol, lipid-lowering medications, diabetes mellitus, systolic and diastolic blood pressure, and use of antihypertensive medications (**Appendix F Figure 47** and **Appendix E Table 22**). However, in the subgroup of men age 70 years or younger, participants with an AHI of 30 or greater were more likely to develop coronary heart disease than those with an AHI less than 5 (adjusted HR, 1.68 [95% CI, 1.02 to 2.76]).

Stroke

One good-quality publication from the SHHS (N=5,422) evaluated the association between AHI and ischemic stroke over a median followup of 8.7 years.[225] Participants in the various AHI categories had median ages of 62 to 75 years, 55 percent were female, and mean BMI was 28 kg/m^2. All participants were untreated for OSA. Incident ischemic strokes occurred in 193 participants. The study separated results by sex (**Appendix E Table 22**). For men, moderate to severe OSA (using AHI ≥19, the highest quartile for the study participants, vs. AHI <4) was associated with ischemic stroke (HR, 2.86 [95% CI, 1.10 to 7.39]). For women, the study did not find a statistically significant association (HR, 1.21 [95% CI, 0.65 to 2.24]). HRs for severe OSA (AHI ≥30) were not reported. The models adjusted for age, BMI, smoking status, systolic blood pressure, use of antihypertensive medications, diabetes status, and race (secondary analyses also addressed atrial fibrillation; including it did not materially change the findings).

Cognitive Impairment or Dementia

One study evaluated the association between AHI and cognitive impairment or dementia among 298 older women (mean age, 82 years).[222] Mean BMI was 28 kg/m^2. Incident mild cognitive impairment or dementia occurred in 107 participants over a mean followup of 4.7 years. Participants with an AHI of 15 or greater had an increased risk of developing cognitive impairment or dementia compared with participants with an AHI less than 15 (OR, 1.85 [95% CI, 1.11 to 3.08]) when adjusted for age, race, BMI, education level, smoking status, presence of diabetes, presence of hypertension, antidepressant use, benzodiazepine use, and use of nonbenzodiazepine anxiolytics. Additional adjustment for baseline cognitive test scores strengthened the association (OR, 2.36 [95% CI, 1.34 to 4.13]).

Although we found no studies evaluating cognitive impairment or dementia per se among men, one study evaluated the association between AHI and *cognitive decline* among 2,636 community-dwelling men age 67 years or older in the Outcomes of Sleep Disorders in Men study.[219] Cognitive decline was assessed using the Trails B and the Modified Mini-Mental State Examination. After 3.4 (median) years of followup, participants with an AHI of 15 or greater did not have an increased risk of cognitive decline compared with participants with an AHI less than 15 using either outcome measure (OR, 1.14 [95% CI, 0.84 to 1.54] and 0.99 [95% CI, 0.79 to 1.24], respectively) when adjusted for age, site, race, BMI, education, number of depressive symptoms, history of diabetes, history of stroke or transient ischemic attack, history of hypertension, history of coronary heart disease, history of Parkinson's disease, impairment in instrumental activities of daily living, benzodiazepine use, antidepressant use, self-reported health status, physical activity, alcohol use, and smoking status.

KQ 7. Harms of Screening or Diagnostic Testing

We found no eligible studies that addressed this question.

KQ 8. Harms Associated With Treatment

Reporting of harms in the included studies was sparse. Most did not report any information about harms. Twenty-two of the RCTs included in KQ 4 reported on harms associated with treatments for OSA. These included nine trials of CPAP,[141,145,150,163,166,167,176,180,183] eight of MADs,[180,189-191,193,195,197,214] one of a very low energy diet,[207] four of airway surgeries,[198,199,201,203] and one of bariatric surgery.[200] Characteristics of all 22 studies have been described in previous sections of this report. Detailed results of studies reporting harms are provided in **Appendix E Tables 23–26**.

CPAP

Of the nine included RCTs, six compared CPAP with a sham device, two compared CPAP with usual care,[180,183] and one compared CPAP with an oral placebo capsule.[176] Most studies enrolled fewer than 100 persons; one study[166] enrolled 281 participants, and the APPLES trial[145] enrolled 1,098 participants. The majority of enrollees were male, mean age ranged from 42 to 61 years, and most participants were overweight or obese (mean BMI, 27 to 39 kg/m^2). Most of the studies followed patients for 8 to 12 weeks. In general, the adverse events related to CPAP treatment were likely short-lived and could be alleviated with discontinuation of CPAP or additional interventions. Overall, 2 to 47 percent of participants in trials reporting any harms had specific adverse events while using CPAP. These included oral or nasal dryness, eye or skin irritation, rash, epistaxis, and pain.

Across four studies,[150,167,180,183] 11 percent of patients receiving therapeutic CPAP reported irritation compared with 1 percent of control patients. In one study,[145] rash was reported by significantly more patients receiving therapeutic CPAP than participants receiving sham (18% vs. 11%; p=0.001). One study reported three nosebleeds: one in the CPAP group (2%) and two in the control group (4%).[183] In two studies, 12 and 47 percent of patients reported oral or nasal dryness in the therapeutic CPAP group compared with no reports in the usual care arm.[176,180] Pain was reported in two trials.[167,176] In one, there was one report each (2%) of ear pain and noncardiac chest pain in the therapeutic CPAP arm; no control patients reported pain.[167] In the other, no active CPAP patients reported pain compared with one control patient (3%) who reported chest and arm pain.[176] None of the studies reported the need for additional sleep medication, excess salivation, or tooth damage or loosening.

MADs

Eight RCTs reported harms of MAD use.[180,189-191,193,195,197,214] Most studies lasted 4 to 6 weeks, one lasted a single week,[214] one lasted 10 weeks,[180] one lasted 12 weeks,[190] and one lasted 24 weeks.[189] Across three studies that reported any discontinuation because of adverse events, 7 percent of active MAD patients discontinued use due to harms compared with 1 percent of control patients.[180,191,197] No studies reported rashes, claustrophobia, nosebleeds, or the need for

additional sleep medications.

In four studies, rates of oral dryness ranged from 5 to 33 percent with active MADs compared with 0 to 3 percent with control.[180,189,190,197] Five studies reported rates of excess salivation.[180,189,190,192,197] Three of these reported excessive salivation rates ranging from 23 to 68 percent in the active treatment arms compared with 0 to 3 percent in the sham or no treatment groups.[180,189,197] One reported a higher rate of excessive salivation in the sham MAD arm than in the active treatment arm (58% and 36%, respectively).[190] The remaining study reported no significant difference in excess salivation between MAD and sham groups but did not report numbers of patients.[192]

All eight RCTs reporting harms included some report of oral mucosal, dental, or jaw symptoms, including mucosal or dental pain, discomfort or tenderness, mucosal erosions, jaw or temporomandibular joint pain or discomfort that occurred either upon waking or persistent, jaw occlusal changes, and jaw muscle discomfort. In seven studies, adverse oral mucosal, dental, or jaw symptoms ranged from 17 to 74 percent in MAD groups compared with 0 to 17 percent in sham, no treatment, or conservative management groups. One study reported only that there was a statistically significant difference in jaw discomfort and tooth tenderness in the MAD group compared with sham.[192]

Airway Surgery

Four included studies assessed harms of surgical treatment: one each of single-session soft palate radiofrequency surgery,[198] TCRFTA,[203] UPPP,[199] and LAUP.[201] Two of the trials had sham surgery comparison groups;[198,203] the rest compared surgery with no treatment or usual care. Sample size was fewer than 70 in all trials, and the majority of patients were male, overweight, and middle aged. No studies reported perioperative death, nerve palsy, need for additional emergency surgery, cardiovascular events, respiratory failure, or airway stenosis.

Overall, less than 1 to 81 percent of participants in trials reporting any harms had harms from surgery. These included postoperative bleeding; rehospitalization; difficulty speaking, breathing, drinking, opening the mouth, and swallowing; change in vocal quality; hematomas; ulcerations; infections; temporary nasal regurgitation; and pain. In the trial that compared LAUP with no treatment,[201] 17 participants (81%) reported moderate to severe pain, nine (33%) reported mild to severe hemorrhaging, one (5%) reported a change in vocal quality, five (24%) reported temporary nasal regurgitation, and four (19%) reported mild infections. In the Sleep Apnoea Karolinska UPPP (SKUP^3) trial,[199] four UPPP patients (13%) reported pain and two (6%) reported postoperative bleeding. In the trial that compared TCRFTA with sham surgery, patients in both arms reported similar increases in pain 1 week after the procedure (up to 1.6 to 1.8 out of 10; difference was not statistically significant). Pain ratings returned to baseline by 3 weeks postprocedure. Rates of other harms did not differ between groups either. There were six reported hematomas: three in the treatment group (12%) and three in the control group (11%), and one ulceration reported in the treatment group. The trial of single-session soft palate radiofrequency surgery[198] reported that participants in the treatment group gave significantly higher ratings of pain, speaking problems, and swelling sensations (within 1 to 6 days after surgery) than sham surgery patients (data not reported, shown in figure only).

Bariatric Surgery

In the trial of bariatric surgery compared with a conventional weight loss program,[200] one surgical patient was rehospitalized because of an acute proximal gastric pouch dilation causing obstructive symptoms and requiring elective laparoscopic replacement of the adjustable gastric banding.

Weight Loss, Diet, and Exercise Interventions

The single weight loss study that reported harms compared a very low energy diet with usual diet over 9 weeks.[207] In the very low energy diet group, less than 10 percent of patients reported each of the following: constipation, elevated alanine aminotransferase concentrations, dizziness, gout, and dry lips.

Chapter 4. Discussion

Summary of Evidence

Table 6 provides a summary of findings in this evidence review. This table is organized by KQ, then by questionnaire, prediction tool, test, or intervention and provides a summary of outcomes along with a description of precision, quality, and applicability.

Evidence for Benefit and Harms of Screening

We did not identify any eligible studies directly evaluating the effectiveness or adverse outcomes of screening for OSA compared with no screening. Potential harms include overdiagnosis and overtreatment for asymptomatic persons (with AHI ≥5) who would never have had symptoms of or problems from OSA and costs and additional testing (e.g., future PSG to follow patients over time). Furthermore, we found no studies evaluating the effect of OSA screening on psychological outcomes such as distress due to labeling or stigma.

Screening Questionnaires and Clinical Prediction Tools

We found very few eligible studies evaluating the accuracy of questionnaires or prediction tools for distinguishing persons in the general population who are more or less likely to have OSA. The only screening approach with at least two included studies suggesting possible accuracy was the MVAP score followed by an in-home PM for detecting *severe* OSAS (AHI ≥30 and ESS >10). AUC was approximately 0.8, with sensitivity around 90 percent and specificity ranging from 72 to 76 percent.[103,104] Although this approach may have promise for screening, the evidence was limited by potential spectrum bias,[233-237] with oversampling of high-risk participants and those with OSA and OSAS, which may substantially overestimate the accuracy that would be achieved in the general population. Such overestimation was illustrated by a study evaluating the Berlin Questionnaire, which reported a reduction in sensitivity from 79 to 37 percent after adjusting for bias in the sampling procedure to report estimated screening properties for the general population.[102] The included studies evaluating MVAP had a high prevalence of OSAS (≥25%),[103,104] OSA (AHI ≥5 for 80% and mean AHI of 22.5),[104] and sleepiness (74%).[103] In addition, none prospectively measured calibration, often assessed by plotting the predicted risk versus an observed event rate,[107] and none assessed clinical utility for improving health outcomes.

We included fewer studies evaluating questionnaires or clinical prediction tools than some previously published reviews and guidelines,[1,8,238] primarily because of our requirement that studies enroll asymptomatic adults or persons with unrecognized symptoms of OSA; referral populations (e.g., to sleep clinics) were not eligible. The focus of previous reviews and guidelines was generally on diagnostic testing (of adults with symptoms suggestive of disordered sleep) rather than on screening (of asymptomatic persons or those with unrecognized symptoms). Nevertheless, those reviews and guidelines generally reported low overall quality/strength of evidence for questionnaires and prediction tools.

Accuracy and Reliability of Diagnostic Tests

We found limited evidence evaluating Type II PMs (3 studies; total of 160 participants). For Type III and IV monitors, existing literature reveals some inconsistency, with wide ranges of sensitivity and specificity (**Table 5**), especially for single-channel Type IV monitors for detecting moderate to severe OSA. Nevertheless, many studies reported moderate to high LR+ (>5) and moderate to low LR- (<0.2), and previous reviews and guidelines concluded that moderate-quality evidence shows that Type III and IV monitors are "generally accurate to diagnose OSA, but have a wide and variable bias in estimating the actual AHI."[1,238] Studies published more recently for Type IV PMs have resulted in greater heterogeneity of methods and findings (than found by prior reviews) and wider ranges of sensitivity and specificity. Evidence for Type IV PMs is limited by inconsistency and imprecision. In addition, unlike other types of PMs, Type IV monitors are limited by their inability to differentiate obstructive and central events. We found scant data addressing reliability of PMs of any type.

Barriers to undergoing diagnostic testing for OSA include limited availability of PSG, ability to tolerate testing, inconvenience, and costs.[239] It is unclear how often those barriers prevent completion of testing. Mean time from referral to sleep clinic evaluation in the United States has wide variation, ranging from a few weeks to more than a year, with longer wait times for university, state, and federal government sleep laboratory facilities.[239] That time may not include the time from clinic evaluation to completion of diagnostic testing, which may occur at a subsequent visit. The majority of diagnostic evaluations are split-night PSG.[239]

Benefits and Harms of Treatment for OSA

Our review found consistent evidence from good- and fair-quality RCTs that CPAP effectively reduces AHI to normal (<5) or near-normal (<10) levels, reduces excessive sleepiness, and reduces blood pressure. However, the clinical significance of mean reductions of 2 points on the ESS and 2 to 3 points for blood pressure measures is somewhat uncertain. For sleepiness, our data suggest a clinically significant reduction in most included trials because 85 percent of the trials in our meta-analysis for ESS that had mean baseline ESS scores of 10 or greater (indicating excessive daytime sleepiness) reported mean endpoint ESS scores in the normal range of less than 10[240,241] for the CPAP groups (mean endpoint ESS <8). However, the threshold for a clinically significant change in ESS is somewhat uncertain. Although recent systematic reviews noted that experts consider a 1-point change in ESS clinically significant,[1] other sources suggest that a greater change, of at least 3 or 4 points, should be the clinically significant threshold. For example, some trials that use ESS as an outcome have considered a 4-point or greater change in ESS as clinically significant for their sample size calculations or interpretation of findings.[242-244] Also, the American College of Chest Physicians' outcome experts evaluating the ESS informally stated that a clinically significant change in the ESS is probably at least 3 points; a specific example cited was that a reduction of 1 point (e.g., from 3 [high] to 2 [moderate]) on two out of seven ESS domains was unlikely clinically relevant.[245] Regardless of what constitutes a clinically significant change, potential bias from the subjective nature of the ESS remains (potential overreporting of improvements in sleepiness after receiving treatment), and some authors have raised concerns about its construct validity (i.e., uncertainty regarding whether it is an accurate measure of sleepiness).[246-248] Multiple studies have reported associations between

sleepiness and health outcomes, although many of them did not use the ESS to measure sleepiness. One study that used the nationwide population-based SHHS[249] (5,816 participants; mean age, 63 years; 52.5% women) reported that excessive daytime sleepiness was strongly associated with reduced quality of life after adjusting for confounding variables (e.g., age, ethnicity) for both sexes. Sleepiness has also been linked to motor vehicle crashes in multiple observational studies.[37,39,250] A cross-sectional study of 913 employed adults from the general U.S. population (enrolled in the WSCS) found that men and women with an AHI greater than 15 were significantly more likely to have multiple accidents over the past 5 years (OR, 7.3 [95% CI, 1.8 to >25], adjusted for age, miles driven, and sex) using state records for motor vehicle accident history (retrospectively).[37] The study was limited by the retrospective design and potential confounding. Considering education and usual alcohol consumption did not alter the OR. However, none of their measures of perceived sleepiness (including those derived from ESS) were significantly related to accident occurrence. A cross-sectional study of 2,342 Australian commercial vehicle drivers found that the sleepiest 5 percent of drivers (based on ESS) had about twice the odds of a self-reported motor vehicle accident over the previous 3 years (OR, 1.91 [95% CI, 1.09 to 3.35]) and even greater odds of multiple accidents over the previous 3 years (OR, 2.67 [95% CI, 1.29 to 5.52]).[250]

For blood pressure reduction, some authors suggest that a difference of more than 9/10 mm Hg (systolic/diastolic) is clinically meaningful for individuals.[251-253] However, across a population, guidelines have suggested that much smaller reductions of 2 to 3 mm Hg for systolic blood pressure could result in a clinically significant reduction in cardiovascular mortality (by 4% to 5% for coronary heart disease and 6% to 8% for stroke).[254]

We found that MADs and weight loss programs also reduce AHI and excessive sleepiness, although the magnitudes of effects were generally less than with CPAP, and blood pressure reduction was not established. Although we did not evaluate head-to-head studies (e.g., directly comparing MADs with CPAP), previous comparative effectiveness reviews examining head-to-head trials reported smaller effect sizes for MADs than for CPAP for reducing AHI.[1] Evidence on surgical treatments was limited by unknown consistency and imprecision, because only a single RCT evaluated each surgical technique studied.

Evidence on most health outcomes was limited (i.e., too few RCTs reported or too few events occurred to make conclusions about the effectiveness for reducing mortality, cardiovascular events, or motor vehicle accidents). However, our meta-analysis for sleep-related quality of life found a significant benefit for CPAP, albeit with a small effect size (SMD, 0.28 [95% CI, 0.14 to 0.42]). The effect size was slightly greater among those with excessive daytime sleepiness at baseline but still small (0.33 [95% CI, 0.17 to 0.50]).

Reporting of harms from treatment in the included studies was sparse. Most did not report any information about harms. In general, the adverse events related to CPAP treatment were likely short-lived and could be alleviated with discontinuation of CPAP or additional interventions. Common adverse effects included oral or nasal dryness, eye or skin irritation, rash, epistaxis, and pain. Common adverse effects from MADs included oral or nasal dryness, excessive salivation, and jaw discomfort. No included studies reported on psychosocial harms of treatment, such as marital stress due to disruption of partner sleeping (e.g., because of the noise of CPAP).

Such adverse effects may limit adherence to treatment. A wide range of adherence to CPAP usage recommendations has been reported, from about 30 to 85 percent.[255] A systematic review for AHRQ's Effective Healthcare Program reported that cohort studies with multivariable analyses for predictors of nonadherence show that 14 to 32 percent of patients discontinue CPAP over 4 years and patients use CPAP for an average of 5 hours per night; data were too limited to provide adherence rates for MADs.[1] The review also found that AHI and ESS are independent predictors of CPAP adherence.[1] A recent Cochrane systematic review of 33 studies (2,047 participants) found low- to moderate-quality evidence that three types of interventions can increase CPAP machine usage in CPAP-naive participants with moderate to severe OSAS.[255] These included supportive interventions that encourage persons to continue to use their CPAP machines, short-term educational interventions, and behavioral therapy. However, they noted that trials did not assess persons who have struggled to adhere to treatment, and the impact of improved CPAP usage on daytime sleepiness, quality of life, and long-term cardiovascular risks remains unclear.

Association Between AHI and Health Outcomes

Consistent, precise evidence from prospective cohort studies that focused on community-based participants supports the association between AHI and all-cause mortality. Although the cohort studies controlled for many potential confounders, residual confounding due to health-related factors that are associated with OSA (e.g., physical activity, diet) and that were generally not accounted for is possible. We found that persons with severe (AHI ≥30) or moderate to severe OSA (AHI ≥15) die at about twice the rate of controls when pooling data from multivariate analyses. We also found consistent evidence showing that persons with severe or moderate to severe OSA have increased cardiovascular mortality. The only studies reporting subgroup analyses suggested that the association may only be present for men age 70 years or younger (but not for women or for men older than age 70 years)[227] and for those with excessive daytime sleepiness.[223] These data do not prove causality, and residual confounding is a possibility, but the included studies were well designed and incorporated many potential confounders in their multivariate analyses.

Limitations

This review is limited in the ability to describe the direct evidence on the effectiveness or harms of screening for OSA because we identified no studies comparing screened and unscreened populations. Therefore, we attempted to review literature that might establish an indirect chain of evidence from multiple questions that link screening to health outcomes (KQs 2 through 8). For the first question in that indirect pathway, we found limited evidence that one screening approach (MVAP followed by an in-home PM) might be useful to screen for severe OSAS, but the evidence was limited by potential spectrum bias, and no studies prospectively assessed calibration or clinical utility for improving health outcomes.

We required studies to use in-laboratory PSG as the reference standard for KQs 2 and 3. This is similar to the approach used in previous systematic reviews. For KQ 2, this resulted in exclusion of a large study from the SHHS that included 4,770 community participants and reported on the

STOP, STOP-Bang, and ESS questionnaires. It reported sensitivity from 39 percent (ESS ≥11) to 87 percent (STOP-Bang) and specificity from 43 percent (STOP-Bang) to 71 percent (ESS) for predicting moderate to severe OSA (respiratory disturbance index ≥15).[256] LR- ranged from 0.3 to 0.85, indicating minimal to small decreases in the likelihood of disease, and LR+ ranged from 1.4 to 1.5, indicating a minimal increase in the likelihood of disease.

We did not evaluate the accuracy of individual physical examination findings. We required questionnaires or clinical prediction tools to have multiple factors because previous systematic reviews have found limited utility of individual findings. A recent review of clinical examination accuracy, which was not limited to asymptomatic patients or those with unrecognized symptoms, found that (among individual symptoms or signs) the most useful observation for identifying patients with OSA was nocturnal choking or gasping, imparting a small increase in the likelihood of disease (summary likelihood ratio, 3.3 [95% CI, 2.1 to 4.6], when the diagnosis was established by AHI ≥10).[8] The review found that many symptoms and signs provide limited information in determining the likelihood of OSA.[8]

We did not evaluate every possible outcome. We chose the outcomes that are most commonly reported and most potentially clinically meaningful. We did not include the Multiple Sleep Latency Test, for example, which was reported by a relatively small number of trials and did not show a clear benefit of CPAP, according to a prior systematic review.[1] For KQ 6, we did not evaluate the association between AHI and incident diabetes. A 2011 systematic review concluded that there may be an association but the strength of evidence was low and the association may be confounded by obesity.[1] A more recent (2014) systematic review concluded that the association between OSA and incident diabetes is uncertain.[92]

Our review was limited to the evaluation of the most common treatments for OSA. We did not evaluate some treatments that may have potential benefits, such as oropharyngeal exercises,[257,258] playing the didgeridoo, or using nasal steroids for treating allergic rhinitis (or similar treatments that might secondarily improve OSA by treating another condition).[259-261] Nevertheless, previous reviews and clinical practice guidelines suggest that the potential benefits of such treatments are limited or uncertain.[1,76]

We limited eligible study designs to RCTs for evaluating treatment benefits. It is possible that this approach excluded some studies that might provide useful evidence for certain treatments, although such evidence has a higher risk of bias because of potential selection bias and confounding. For example, the Swedish Obesity Study was a nonrandomized study that included almost 3,500 participants.[262] Over 2-year followup after bariatric surgery, it found marked improvement in sleep apnea symptoms for patients treated with bariatric surgery than for a conservatively treated control group. Other examples include observational studies focused on motor vehicle accidents. A meta-analysis of such observational studies that evaluated the association between CPAP and motor vehicle accidents identified nine retrospective before-after studies, all without control groups (and all studies we consider to have a high risk of bias mainly because of the risk of selection bias and confounding), and reported a reduction in crash risk following treatment (risk ratio, 0.28 [95% CI, 0.22 to 0.35]).[263] A recent observational study that used the Swedish Traffic Accident Registry reported that CPAP use for 4 or more hours per night was associated with a reduction of accident incidence (from 7.6 to 2.5 accidents/1,000

drivers/year).[264]

Some of our meta-analyses of RCTs evaluating benefits of CPAP (KQ 4) found substantial statistical heterogeneity. We did not find a clear explanation for the statistical heterogeneity, but possible explanations include variation in CPAP devices (e.g., machines, masks, humidifiers, filters, cushions), participant characteristics (e.g., studies with lower baseline mean AHI finding smaller effect sizes because of ceiling effects), apnea and hypopnea definitions, adherence, study duration, study methods, or chance. Definitions of apnea and hypopnea vary in published studies. For example, various cutpoints for oxygen desaturation are used to define hypopnea; some studies define hypopnea as requiring either oxygen desaturation or an electroencephalogram arousal, and some studies do not clearly define hypopnea. A publication from the SHHS demonstrated the potential impact of variation in hypopnea definitions on prevalence of OSA, reporting that varying the definition in an otherwise healthy older population resulted in the prevalence increasing from roughly 50 percent (using the Centers for Medicare & Medicaid Services definition of 4% oxygen desaturation) to greater than 80 percent (using the American Academy of Sleep Medicine 2012 definition of either a 3% oxygen desaturation or an electroencephalogram arousal).[265,266] We did not abstract detailed information about apnea and hypopnea definitions from each study and did not conduct subgroup analyses or meta-regression to explore the specific contribution of every possible factor that may explain some of the statistical heterogeneity identified by our meta-analyses. Regardless of the cause of the statistical heterogeneity, all trials reported statistically significant improvement for AHI (with endpoint AHI values universally ≤10 for CPAP-treated groups), and the vast majority of trials that included participants with excessive daytime sleepiness at baseline (ESS ≥10) reported mean endpoint ESS scores well into the normal range (<8) for the CPAP-treated groups.

For the association between AHI and health outcomes, it is unclear whether some of the studies excluded central apnea from their analyses, and it is possible that central apnea may account for some small portion of the reported associations between AHI and health outcomes. Of note, one publication from the SHHS reported that the association between AHI and incidental myocardial infarction was due to increases in both obstructive and central apnea events.[267] However, predominant central apnea is relatively rare, seen in less than 10 percent of patients presenting for PSG and in less than 1 percent of the general population.[16,17] Among the studies in our meta-analysis analyzing the relationship between AHI and all-cause mortality, two studies reported no information about central events (and it is unclear whether central events were included in their analyses),[220,229] one reported just that there were few central events,[226] and two provided more detailed results.[223,227] Among those that provided more detailed results, one reported data from the SHHS and found that the central apnea index was not associated with mortality in men or women,[227] and the other reported that a sensitivity analysis excluding the 4 percent of patients with predominately central apnea resulted in no meaningful change in findings.[223]

For harms of treatment (KQ 8), we required studies to have a control group to be eligible. This resulted in the exclusion of large uncontrolled observational studies, which may be useful for determining rates of harms from surgical procedures. For example, a large study of patients who underwent UPPP reported a 0.2 percent (7/3,130) perioperative mortality rate and a serious complication rate of 1.6 percent (51/3,130), including reintubation, pneumonia, hemorrhage, cardiovascular complication, emergency tracheotomy, and mechanical ventilation for more than

48 hours.[268] Such evidence has been summarized elsewhere.[1]

Future Research Needs

To better understand the potential effectiveness of screening for OSA, randomized trials of asymptomatic persons (or those with unrecognized symptoms) that directly compare screening with no screening and assess health outcomes are needed (i.e., trials that address KQ 1, the overarching question). To better determine the accuracy of screening questionnaires and clinical prediction tools when used in the general population (related to our KQ 2), additional studies are needed; such studies should aim to include a representative community population, to avoid spectrum bias, and to further evaluate promising screening approaches (e.g., MVAP followed by in-home PM) as well as other approaches for which we found limited or no eligible studies, such as the STOP-Bang Questionnaire. A recently published systematic review and meta-analysis concluded that the STOP-Bang Questionnaire has good performance for screening for OSA in sleep clinic and surgical populations.[269] However, it did not identify studies with representative community populations that compared STOP-Bang with PSG. Of the 17 included studies, 11 were from sleep clinic populations (not eligible for our review), three were from surgical populations, and three were from other populations. Of the three from surgical populations, we excluded one because of poor quality,[69] one because of ineligible comparator[70] as it compared STOP-Bang findings with a PM (rather than PSG), and one because of ineligible country[270] (a small study of 40 patients undergoing coronary artery bypass graft or abdominal surgery in Brazil). Of the three studies from other populations, one was from the general population, one from bus drivers, and one from patients with renal failure. These were excluded from our review for the following reasons: ineligible comparator (it compared findings with a PM),[256] ineligible country (study of 85 Turkish bus drivers),[271] and ineligible comparison (it compared findings with a PM among 172 patients with renal failure).[272]

More studies are needed that assess the reliability of PMs for home use, particularly studies that enroll patients representative of the general population. Trials are needed that evaluate whether CPAP and other common treatments improve health outcomes (except for sleep-related quality of life), such as cardiovascular events. Studies are needed that determine whether findings (for diagnostic test accuracy and treatment benefits) differ for subgroups defined by age, sex, BMI, or OSA severity.

Two documents produced for AHRQ's Effective Healthcare Program specifically address future research needs related to diagnosis[273] and treatment[274] of OSA. To determine priorities, the authors engaged 21 to 22 panel members representing patients and the public, providers, purchasers of health care, payers, policymakers, and principal investigators. Some of the high-priority future research needs that are relevant to our review included determination of the prognostic accuracy of clinical prediction rules to predict clinical outcomes; assessment of the impact of treatment on major long-term clinical outcomes, including mortality, cardiovascular disease, and diabetes; and trials of different sleep apnea treatments based on patient characteristics (trials of CPAP and non-CPAP treatments stratified by disease severity).

Conclusion

There is uncertainty about the clinical utility of all potential screening tools. Although screening with MVAP followed by an in-home PM may have promise for accurately distinguishing persons in the general population who are more or less likely to have OSA, current data are limited by potential spectrum bias, with oversampling of high-risk participants and those with OSA and OSAS. Further, we found no studies that prospectively evaluated screening questionnaires or clinical prediction tools to report calibration or clinical utility for improving health outcomes. Multiple treatments for OSA improve intermediate outcomes—CPAP effectively reduces AHI to normal or near-normal levels, reduces excessive sleepiness, and reduces blood pressure; MADs and weight loss programs also reduce AHI and excessive sleepiness, although the magnitudes of effects were generally less than with CPAP. Although good evidence has established that persons with severe or moderate to severe OSA die at twice the rate of controls, trials of CPAP and other treatments have not satisfactorily evaluated whether treatment reduces mortality or improves most other health outcomes, barring evidence of some possible benefit for sleep-related quality of life.

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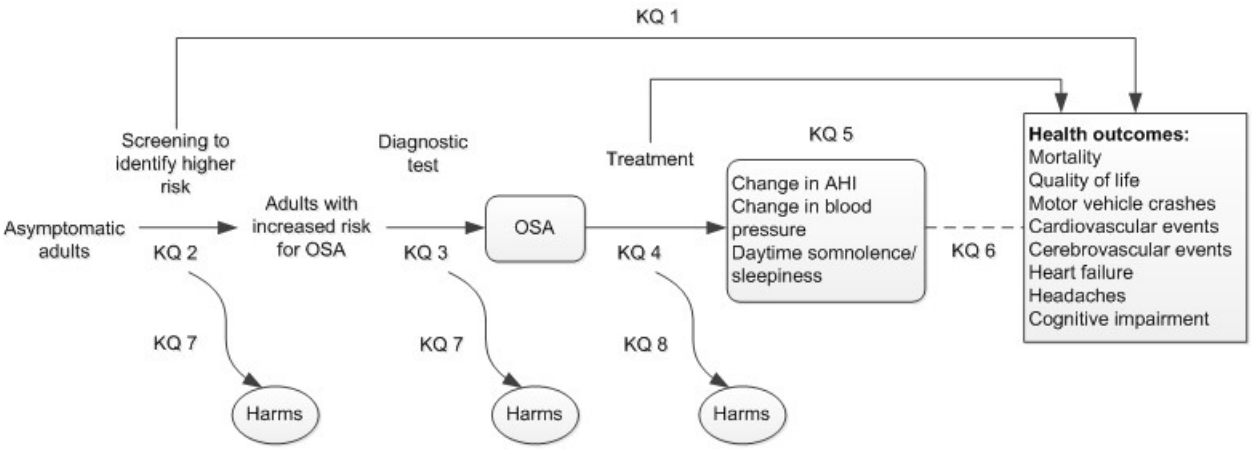
Figure 1. Analytic Framework

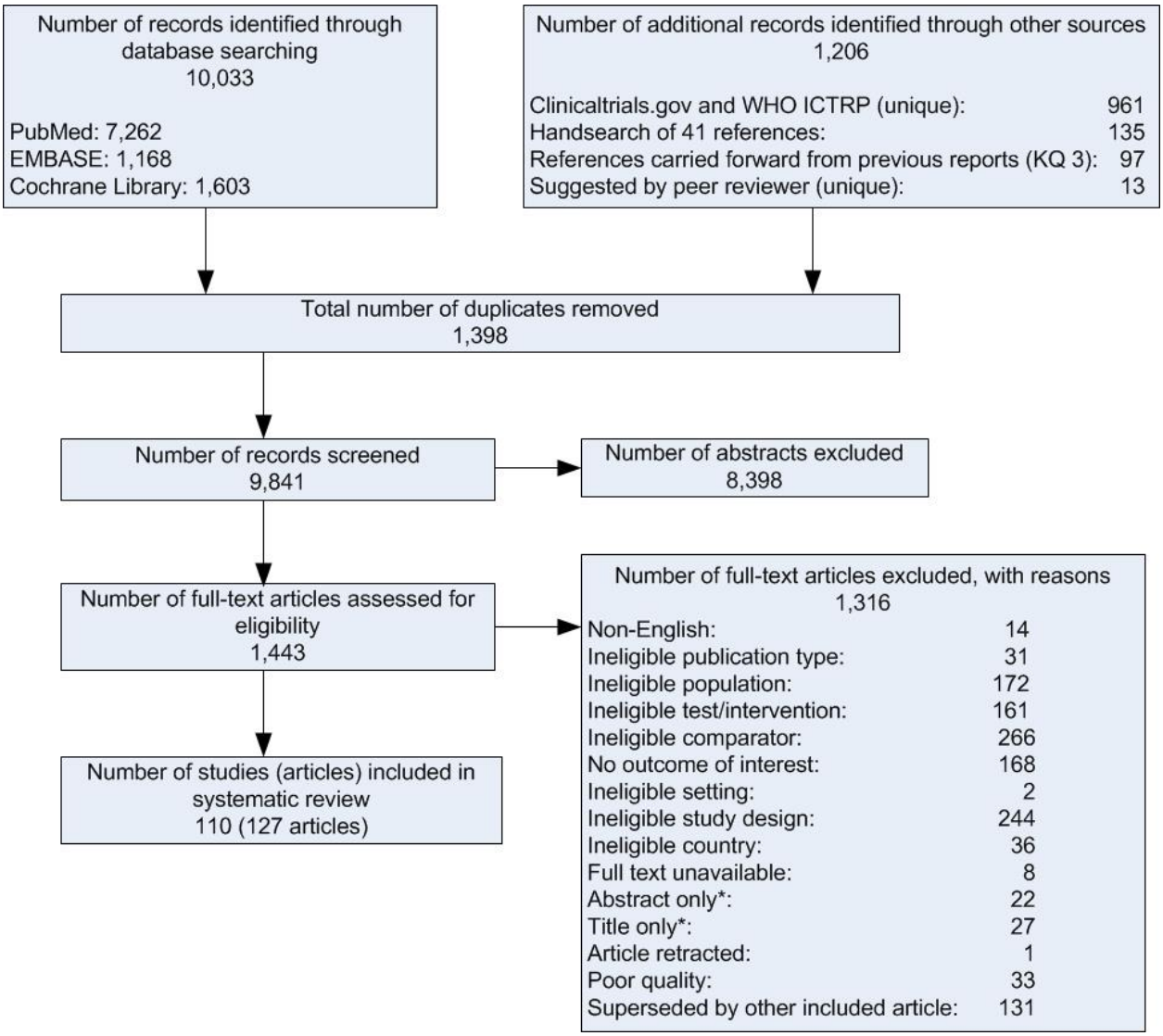


Abbreviations: AHI=apnea-hypopnea index; KQ=Key Question; OSA=obstructive sleep apnea.

Key Questions to Be Systematically Reviewed

1a. Does screening for obstructive sleep apnea (OSA) in adults improve health outcomes?
1b. Does the evidence on screening for OSA in adults differ for subgroups defined by age, sex, body mass index (BMI), or OSA severity?
2a. What is the accuracy of currently existing clinical prediction tools or screening questionnaires in identifying persons in the general population who are more or less likely to have OSA?
2b. What is the accuracy of multistep screening approaches, such as using a questionnaire or prediction tool followed by overnight home-based testing, in identifying persons in the general population who are more or less likely to have OSA?
3a. What is the accuracy and reliability of diagnostic tests for OSA?
3b. Do the accuracy and reliability of diagnostic tests for OSA differ for subgroups defined by age, sex, or BMI?
4a. How much does treatment with continuous positive airway pressure (CPAP), mandibular advancement devices, surgery, or weight loss programs improve intermediate outcomes (i.e., the apnea-hypopnea index [AHI], blood pressure, or sleepiness) in persons with OSA?
4b. Do the benefits of treatment (for intermediate outcomes) differ for subgroups defined by age, sex, BMI, or OSA severity?
5a. Does treatment with CPAP, mandibular advancement devices, surgery, or weight loss programs improve health outcomes in persons with OSA?
5b. Do the benefits of treatment (for health outcomes) differ for subgroups defined by age, sex, BMI, or OSA severity?
6. Is there an association between AHI and health outcomes?
7a. Are there harms associated with screening or diagnostic testing for OSA?
7b. Do the harms of screening or diagnostic testing differ for subgroups defined by age, sex, or BMI?
8a. Are there harms associated with treatment of OSA?
8b. Do the harms of treatment differ for subgroups defined by age, sex, BMI, or OSA severity?

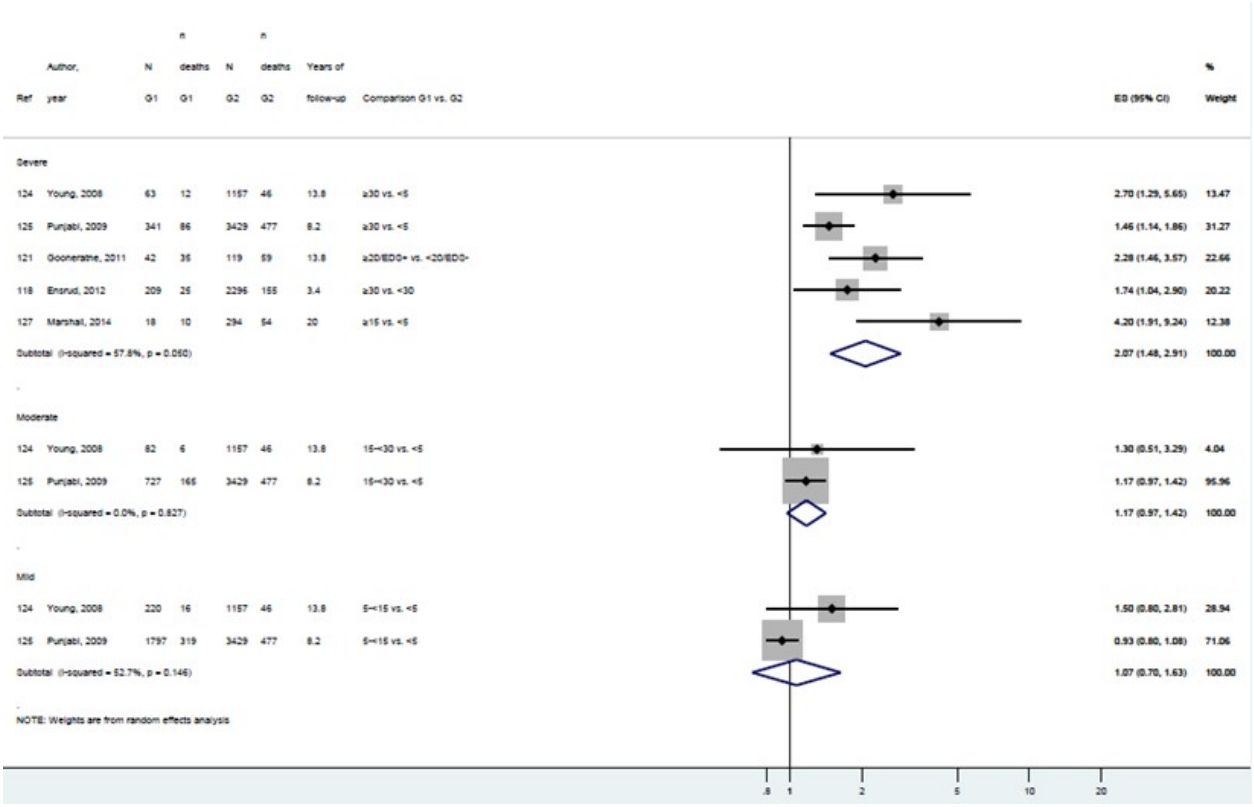
Figure 2. Summary of Evidence Search and Selection



* Insufficient information to assess risk of bias.

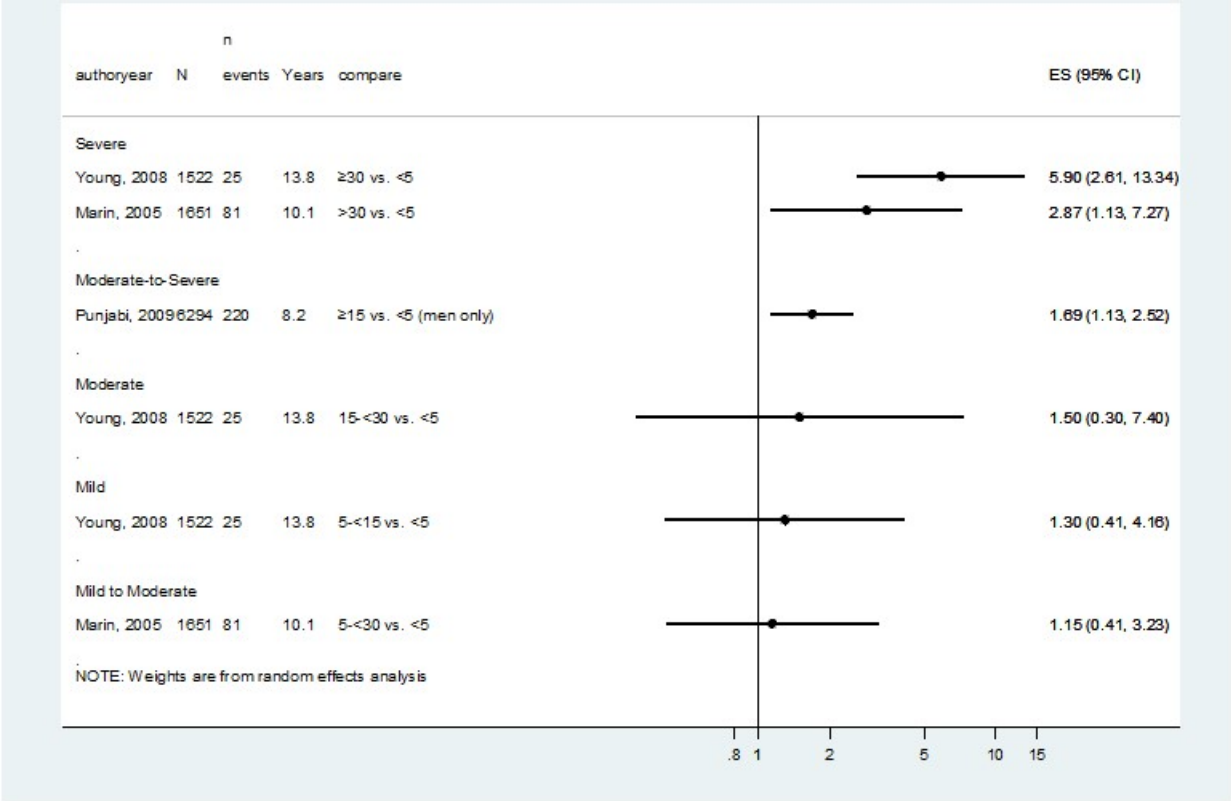
Abbreviations: KQ=Key Question; WHO ICTRP=World Health Organization International Clinical Trials Registry Platform.

Figure 3. Association Between AHI and All-Cause Mortality, by OSA Severity



Abbreviations: AHI=apnea-hypopnea index; OSA=obstructive sleep apnea.

Figure 4. Association Between AHI and Cardiovascular Mortality, by OSA Severity



Abbreviations: AHI=apnea-hypopnea index; OSA=obstructive sleep apnea.

Table 1. Definitions

Term	Definition
Apnea	Cessation of airflow for at least 10 seconds[8,275]
Hypopnea	Reduction in airflow by at least 30% for at least 10 seconds with decrease in oxygen saturation
Apnea-hypopnea index (AHI)*	Number of apnea and hypopnea events per hour of sleep
Obstructive sleep apnea (OSA)	
Mild[8,73]	AHI ≥5 to <15
Moderate[8,73]	AHI ≥15 to <30
Severe[8,73]	AHI ≥30
Obstructive sleep apnea syndrome	AHI ≥5 with evidence of daytime sleepiness[3,8,276]

*The respiratory disturbance index (RDI) is a similar measure to AHI, but it also includes the number of respiratory effort–related arousals per hour of sleep (in addition to apnea and hypopnea events).
Abbreviations: AHI=apnea-hypopnea index; OSA=obstructive sleep apnea; RDI=respiratory disturbance index.

Table 2. Classification of Monitors Used for Diagnosis of Obstructive Sleep Apnea*

Type	Portability	Number of Channels	Typical Parameters	≥2 Airflow or Effort Channels	Measures AHI
I	Facility-based	≥7 (Usually 12–16)	EEG, EOG, EMG, ECG/HR, airflow (nasal and/or oral), respiratory effort (thoracic or abdominal movement), SaO_2, body position, leg movement, snoring	Yes	Yes
II	Portable	≥7	EEG, EOG, EMG, ECG or HR†, airflow, respiratory effort (thoracic or abdominal movement), SaO_2	Yes	Yes
III	Portable	≥4 (Usually 4–7)	Ventilation and/or airflow, respiratory effort (thoracic or abdominal movement), ECG or HR, SaO_2	Yes	No
IV	Portable	≥1 (Usually 1–3)	Usually SaO_2‡; may include additional channels provided the monitor doesn't qualify as Type III§	No	No

* Modified with permission from a previous systematic review[1]; personal communication with Dr. Ethan Balk, October 5, 2015.

† Heart rate is allowed in place of electrocardiogram in Type II portable monitors. Type II monitors usually measure the same channels as Type I monitors but are portable.

‡ Unlike other monitor types that measure SaO_2 by oximetry, Type IV monitors may measure SaO_2 by oximetry and/or airflow.

§ Parameters that are more commonly measured by Type IV portable monitors include but are not limited to snoring, body position, leg movement, peripheral arterial tone, and plethysmograph.

Abbreviations: AHI=apnea-hypopnea index; ECG=electrocardiogram; EEG=electroencephalogram; EMG=electromyogram; EOG=electrooculogram; HR=heart rate; SaO_2=arterial O_2 saturation.

Table 3. Characteristics of Included Studies for KQ 2

First Author, Year Country Study Design	N	Participants	Questionnaire/ Tool Name	Questionnaire/ Tool Components	Mean Age (Range)	% F	% Non-white	Mean BMI	Mean AHI	% HTN % HF	% With OSA	Quality
Gurubhagavatula, 2013[104] United States Cross-sectional	250	Those with HTN* from internal medicine practices and a HTN clinic	Single-stage models used the MVAP score; two-stage models used MVAP plus AHI from home test	MVAP combined symptoms of snoring, choking, and witnessed apnea with BMI, age, and sex	53 (NR)	20	60	32.1	22.5	100 NR	Of the 79% who had in-lab PSG: Any: 80 Mild: 34 Moderate: 22 Severe: 25 % OSAS: Mild: 25 (AHI ≥5 and ESS >10) Severe: 7.6 (AHI ≥30 and ESS >10)	Fair
Morales, 2012[103] United States Cross-sectional	452	Medicare recipients from the greater Philadelphia metro region, most with some daytime sleepiness†	Single-stage models used the MVAP score; two-stage models used MVAP plus AHI from home test	MVAP combined symptoms of snoring, choking, and witnessed apnea with BMI, age, and sex	71 (NR)	70	64	30	NR	NR 0	Any OSAS (AHI ≥5 and ESS >10): 27 Mild (AHI 5–15 and ESS >10): 9 At least moderate (AHI ≥15 and ESS >10): 17 Moderate (AHI 15–30 and ESS >10): 8 Severe (AHI ≥30 and ESS >10): 8	Fair
Hrubos-Strom, 2011[102] Norway Cross-sectional	16,302 completed the BQ; 518 had PSG	Randomly drawn from national population register	BQ (Norwegian translation)	10 questions on snoring, witnessed apnea, fatigue or sleepiness, and blood pressure; and height, weight, age, and sex	Screening sample: 48 (NR) Clinical sample: 48 (NR)	53 45	NR NR	26 28	NA Median, 6.4	14 27 NR NR	NR	Fair

* Required to have blood pressure ≥140/90 mm Hg or to be on antihypertensive medications.
† From personal communication with Indira Gurubhagavatula (July 2015), 74% met their definition of daytime sleepiness (frequency of sleepiness, based on whether they had a problem staying awake, of every day or several [≥3] days per week); 32% had ESS >10.

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; BQ=Berlin Questionnaire; ESS=Epworth Sleepiness Scale; F=female; HF=heart failure; HTN=hypertension; KQ=Key Question; MVAP=Multivariable Apnea Prediction; N=sample size; NR=not reported; OSA=obstructive sleep apnea; PSG=polysomnography.

Table 4. Results of Included Studies: Accuracy of Screening Questionnaires and Clinical Prediction Tools (KQ 2)

First Author, Year	Questionnaire/Tool Name Cutoff Value	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Calibration	Others
Gurubhagavatula, 2013[104]	MVAP to predict severe OSAS (AHI ≥30 and ESS >10) 0.483	91.5 (NR)	43.9 (NR)	0.684 (0.668 to 0.700)	NR	Neg LR, 0.190 NPTP=0.015
Gurubhagavatula, 2013[104]	MVAP to predict any OSAS (AHI ≥5 and ESS >10) 0.559	69.4 (NR)	56.5 (NR)	0.614 (NR)	NR	Neg LR, 0.524 NPTP=0.148
Gurubhagavatula, 2013[104]	MVAP + uAHI* to predict severe OSAS (AHI ≥30 and ESS >10) uAHI 18	88.2 (NR)	71.6 (NR)	0.799 (0.777 to 0.822)	NR	Neg LR, 0.162 NPTP=0.015
Gurubhagavatula, 2013[104]	MVAP + uAHI* to predict any OSAS (AHI ≥5 and ESS >10) uAHI 13.5	80.5 (NR)	54.0 (NR)	0.672 (NR)	NR	Neg LR, 0.349 NPTP=0.104
Morales, 2012[103]	MVAP to predict severe OSAS (AHI ≥30 and ESS >10) 0.49	90.0 (NR)	64.4 (NR)	0.776 (0.710 to 0.846)	NR	Neg LR, 0.141 NPTP=1.1%
Morales, 2012[103]	MVAP + uAHI* to predict severe OSAS (AHI ≥30 and ESS >10) uAHI 15	90.9 (NR)	75.7 (NR)	0.833 (0.765 to 0.902)	NR	Neg LR, 0.120 NPTP=1.0%
Hrubos-Strom, 2011[102]	BQ to predict AHI ≥5[†] BQ high risk vs. low risk	37.2 (36.0 to 38.4)	84.0 (83.2 to 84.7)	NR	NR	PPV (95% CI), 61.3 (59.7 to 62.9) NPV (95% CI), 66.2 (65.3 to 67.1) Pos LR (95% CI), 2.3 (2.2 to 2.5) Neg LR (95% CI), 0.8 (0.7 to 0.8)
Hrubos-Strom, 2011[102]	BQ to predict AHI ≥15[†] BQ high risk vs. low risk	43.0 (41.2 to 44.8)	79.7 (79.0 to 80.5)	NR	NR	PPV (95% CI), 33.5 (32.0 to 35.0) NPV (95% CI), 85.5 (84.8 to 86.1) Pos LR (95% CI), 2.1 (2.0 to 2.3) Neg LR (95% CI), 0.7 (0.7 to 0.7)

* 2-stage process using MVAP for everyone, and then home testing to determine AHI for those with an intermediate MVAP score.
[†] Estimates were based on a simulated model that adjusted for oversampling of BQ high-risk subjects (not just based on findings for the 518 in the clinical sample).

Abbreviations: AHI=apnea-hypopnea index; AUROC=area under the receiver operating characteristic curve; BMI=body mass index; BQ=Berlin Questionnaire; CI=confidence interval; ESS=Epworth Sleepiness Scale; KQ=key question; MVAP=Multivariable Apnea Prediction; N=sample size; Neg LR=negative likelihood ratio; NPTP=negative posttest probability; NPV=negative predictor value; NR=not reported; OSA=obstructive sleep apnea; OSAS=obstructive sleep apnea syndrome; Pos LR=positive likelihood ratio; PPV=positive predictive value; uAHI=unattended AHI from home sleep test.

Table 5. Summary of Accuracy of Diagnostic Tests for Obstructive Sleep Apnea

	PSG AHI ≥5			PSG AHI ≥15			PSG AHI ≥30		
Portable Monitor	**Sn (%)**	**Sp (%)**	**AUC (%)**	**Sn (%)**	**Sp (%)**	**AUC (%)**	**Sn (%)**	**Sp (%)**	**AUC (%)**
Type II	88-96	50-84	86-90	85-94	77-95	89-94	64-86	98-100	85
Type III	87-96	60-76	89-96	49-92	79-95	85-97	50-97	90-93	86-99
Type IV	65-100	35-100	NR*	7-100	15-100	NR†	NR‡	NR§	NR‖

* The 2011 systematic review did not report the range of AUC values for the 2007 technology assessment and articles newly included in the 2011 review. The AUC values among the 13 studies newly identified since the 2011 review ranged from 59 to 94.

† The 2011 systematic review did not report the range of AUC values for the 2007 technology assessment and articles newly included in the 2011 review. The AUC values among the 13 studies newly identified since the 2011 review ranged from 89 to 96.

‡ The 2011 systematic review did not report the range of Sn values for the 2007 technology assessment and articles newly included in the 2011 review. The Sn values among the 13 studies newly identified since the 2011 review ranged from 59 to 100.

§ The 2011 systematic review did not report the range of Sp values for the 2007 technology assessment and articles newly included in the 2011 review. The Sp values among the 13 studies newly identified since the 2011 review ranged from 71 to 100.

‖ The 2011 systematic review did not report the range of AUC values for the 2007 technology assessment and articles newly included in the 2011 review. The AUC values among the 13 studies newly identified since the 2011 review ranged from 73 to 95.

Abbreviations: AHI=apnea-hypopnea index; AUC=area under the curve; NR=not reported; PSG=polysomnography; Sn=sensitivity; Sp=specificity.

Table 6. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

Questionnaire/Tool (KQ 2), Test (KQ 3), Intervention (KQs 4, 5, 8), or Outcome (KQ 6)	No. of Studies and Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
KQ 1. Does screening for OSA in adults improve health outcomes?							
No studies identified							
KQ 2a. What is the accuracy of currently existing clinical prediction tools or screening questionnaires in identifying persons in the general population who are more or less likely to have OSA?							
Berlin Questionnaire	1 cross-sectional (16,302 completed Berlin; 518 had PSG)	Sn and Sp (95% CI), estimated for the general population (adjusted for oversampling high-risk participants): AHI ≥5: 37.2% (36.0 to 38.4); 84% (83.2 to 84.7) AHI ≥15: 43% (41.2 to 44.8); 79.7% (79.0 to 80.5)	Unknown, single study Precise	Undetected	Fair	Single study that has not been externally validated; moderate risk of bias due to missing data, attrition bias, spectrum bias	General population of Norway
MVAP score	2 cross-sectional (702)	For *severe* OSAS (AHI ≥30 and ESS >10) using MVAP cutoff 0.48 to 0.49: Sn (95% CI): 90% (NR) to 91.5% (NR) Sp (95% CI): 43.9% (NR) to 64.4% (NR) AUC (95% CI): 0.68 (0.67 to 0.70) to 0.78 (0.71 to 0.85)	Inconsistent (one with inadequate discrimination; one with reasonable discrimination) Imprecise	Undetected	Fair	Concern for spectrum bias in both studies; risk of attrition bias in one	Populations with high prevalence of OSAS (≥25%); only one of the studies reported % with any OSA (80%); studies included Medicare recipients and adults with hypertension
MVAP score	1 cross-sectional (250)	For *any* OSAS (AHI ≥5 and ESS >10) Sn (95% CI): 69.4% (NR) Sp (95% CI): 56.5% (NR) AUC (95% CI): 0.614 (NR)	Unknown Imprecise	Undetected	Fair	Concern for spectrum bias; risk of attrition bias	Populations with high prevalence of OSAS; studies included Medicare recipients and adults with hypertension
KQ 2b. What is the accuracy of multistep screening approaches, such as using a questionnaire or prediction tool followed by overnight home-based testing, in identifying persons in the general population who are more or less likely to have OSA?							
MVAP followed by home PM	2 cross-sectional (702)	For *severe* OSAS (AHI ≥30 and ESS >10) using home-based AHI of 15 or 18: Sn (95% CI): 88.2% to 90.9% (NR) Sp (95% CI): 71.6% to 75.7% (NR) AUCs: 0.799 (0.777 to 0.822) and 0.833 (0.765 to 0.902)	Consistent Precise	Undetected	Fair	Concern for spectrum bias; risk of attrition bias in one	Populations with high prevalence of OSAS; studies included Medicare recipients and adults with hypertension
MVAP followed by home PM	1 cross-sectional (250)	For *any* OSAS (AHI ≥5 and ESS >10) Sn (95% CI): 80.5% (NR) Sp (95% CI): 54.0% (NR) AUC (95% CI): 0.672 (NR)	Unknown Imprecise	Undetected	Fair	Concern for spectrum bias; risk of attrition bias	Populations with high prevalence of OSAS; studies included Medicare recipients and adults with hypertension

Table 6. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

Questionnaire/Tool (KQ 2), Test (KQ 3), Intervention (KQs 4, 5, 8), or Outcome (KQ 6)	No. of Studies and Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
KQ 3. What is the accuracy of diagnostic tests for OSA?							
Type II PMs	3 (160)	Sn/Sp: Some wide ranges across multiple AHI cutpoints, with a majority being moderate to high AUC: High discriminatory accuracy (85% to 94%) across multiple AHI cutpoints LR: Majority were moderate to high across AHI cutpoints	Reasonably consistent Imprecise	Undetected	Fair	Small sample size; missing data (complete cases only); not all reported independent scoring	Those suspected of having OSA; referral populations
Type III PMs	1 SR of 19 studies (1,507); 2 newer studies (184)	Sn/Sp: Some wide ranges across multiple AHI cutpoints; majority being moderate to high AUC: 85% to 99% across multiple AHI cutpoints LR: High for in-lab evaluations but lower and more varied for at-home evaluations	Reasonably consistent Imprecise	Undetected	Good	Heterogeneity of results across PM settings (in lab, at home) and for more severe OSA	Those suspected of having OSA; referral population
Type IV PMs	1 SR of 70 studies (6,873*); 14 newer studies (1,900)	Sn/Sp: Wide range across multiple AHI cutpoints AUC: High discriminatory accuracy in diagnosing OSA (most >80%) across multiple AHI cutpoints, regardless of number of PM channels LR: Majority were moderate to high across AHI cutpoints	Inconsistent Imprecise	Undetected	Fair	Heterogeneity of scoring methods and criteria, PM AHI cutpoints; handling of missing data; not all reported independent scoring	Those suspected of having OSA; referral population
KQ 3. What is the reliability of diagnostic tests for OSA?							
Type II PMs	2 (78)	Good to very good kappas for dual scoring of PM and PSG data; high OSA staging concordance and low AHI variability between scorers	Reasonably consistent Imprecise	Undetected	Fair	Small sample size; not all scoring was blinded	Those suspected of having OSA; referral population
Type III PMs	No studies identified						
Type IV PMs	1 (15)	Very good interobserver agreement for manual scoring of PM results	Unknown Imprecise	Undetected	Fair	Single study; small sample size	Those suspected of having OSA; referral population

Table 6. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

Questionnaire/Tool (KQ 2), Test (KQ 3), Intervention (KQs 4, 5, 8), or Outcome (KQ 6)	No. of Studies and Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
KQ 4. How much does treatment improve intermediate outcomes in persons with OSA?							
CPAP[†]	AHI: 19 RCTs (837) ESS: 34 RCTs (5,209) BP: 29 RCTs reported any measure	AHI CPAP vs. Sham: WMD, -33.8 (95% CI, -42.0 to -25.6; 13 trials; N=543) ESS CPAP vs. Sham: WMD, -2.0 (95% CI, -2.6 to -1.4; 22 trials; N=2,721) BP Diurnal SBP: WMD, -2.4 (95% CI, -3.9 to -0.9; 15 trials; 1,190 participants) Diurnal DBP: WMD, -1.3 (95% CI, -2.2 to 0.4); reduction in 24-hour mean arterial pressure about 2 points	Consistent for AHI and BP; inconsistent for ESS Precise	Undetected	Fair to good	Most trials were ≤12 weeks; for ESS, substantial heterogeneity in some meta-analyses, self-report, and validity	Referral population with known OSA
Mandibular advancement devices[†]	AHI: 10 RCTs (616) ESS: 9 RCTs (562) BP: 5 RCTs reported any measure (349)	AHI MAD vs. Sham: WMD, -12.6, (95% CI, -15.5 to -9.7; 6 trials, N=307) ESS MAD vs. Sham: WMD -1.5 (95% CI, -2.8 to -0.2; 5 trials; N=267) BP No significant reduction in any BP measures	Consistent Precise for AHI, imprecise for ESS and BP	Undetected	Good for AHI and ESS, fair for BP	Heterogeneity of BP measures and analyses; low or NR rates of HTN at baseline for those analyses	Referral population with known OSA
Airway surgery	AHI: 5 RCTs (254) ESS: 4 RCTs (187) BP: 1 RCT (46)	AHI: trials of UPPP and LAUP found benefit ESS: no benefit BP: no significant change in either group	Unknown Imprecise	Undetected	Fair	Just 1 trial for each of 5 different surgeries (N= 32 to 67)	Potentially limited; OSA patients from ENT clinics, sleep clinics, or referrals; those deemed good candidates for surgery
Bariatric surgery	AHI: 1 RCT (60) ESS: 1 RCT (60) BP: 1 RCT (60)	No significant difference between groups	Unknown Imprecise	Undetected	Fair		Potentially limited; morbidly obese candidates for bariatric surgery
Weight loss programs	AHI: 5 RCTs (477) ESS: 4 RCTs (213) BP: 3 RCTs (184)	AHI: WMD, -12.4 (95% CI, -19.4 to -5.5) ESS: WMD, -3.4 (95% CI, -5.9 to -1.0); 3/4 trials found reductions, ranging from -3 to -7 BP: no significant difference between groups	Some inconsistency Precise for AHI and ESS; imprecise for BP	Undetected	Fair to good	For BP: 3 different interventions studied; very wide qualitative CI	Obese men and women, generally with moderate to severe OSA

Table 6. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

Questionnaire/Tool (KQ 2), Test (KQ 3), Intervention (KQs 4, 5, 8), or Outcome (KQ 6)	No. of Studies and Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
KQ 5. How much does treatment improve health outcomes in persons with OSA?							
CPAP[‡]	Mortality: 31 RCTs (2,673) SF-36 PCS: 7 RCTs (616) SF-36 MCS: 8 RCTs (978) EQ-5D: 2 RCTs (663) Sleep-related QOL (SAQLI or FOSQ): 13 RCTs (2,325) MVA: 3 RCTs (1,595) CBV events: 4 RCTs (1,604) CV events: 8 RCTs (1,529) HF: 1 RCT (723)	Mortality: No events (27 RCTs) or 1 event (2 RCTs) at ≤12 weeks; no proven benefit at 24 weeks (1 RCT: 2 vs. 2) or 4 years (1 RCT: 8 vs. 3) SF-36 PCS: CPAP vs. any comparator: WMD, 2.3 (95% CI, 0.2 to 4.4); 7 trials; N=648 SF-36 MCS: CPAP vs. any comparator: WMD, 1.2 (95% CI, -0.8 to 3.2); 8 trials; N=1,039 EQ-5D: No benefit (1 RCT); insufficient data provided to determine between group differences (1 RCT) SAQLI or FOSQ: CPAP vs. any comparator: SMD, 0.28 (95% CI, 0.14 to 0.42); 13 trials; N=2,325 MVA: No benefit across 3 RCTs CBV events: Overall, too few events were observed to draw conclusions[§] CV events: Overall, too few events were observed to draw conclusions, but trend in direction favoring CPAP[‖]	Mortality, CBV and CV events: Consistent for studies of relatively short duration (≤12 to 24 weeks); unknown for longer duration SF-36 PCS, MCS, and NHP: Inconsistent EQ-5D, heart failure: unknown Sleep-related QOL, MVA, TIA: Consistent Precise for sleep-related QOL (SAQLI and FOSQ); imprecise for all other outcomes	Detected for SF-36 outcomes (5 RCTs only reported on individual SF-36 domains but not overall, PCS, or MCS scores) Undetected for all other outcomes	Fair	Study duration may be insufficient to determine benefit for many health outcomes; small number of total events observed across studies (for mortality, MVA, CBV, and CV events)	Referral population with known OSA
Mandibular advancement devices	Mortality: 4 RCTs (245) SF-36 total: 1 RCT (97) SF-36 PCS: 2 RCTs (183) SF-36 MCS: 2 RCTs (183) Sleep-related QOL: 3 RCTs (256) MVA: 1 RCT	One total death in no-treatment group in one 4-week RCT (N=93); mixed results for QOL measures; 5 total MVA events (3 in MAD groups and 2 in no treatment groups)	Inconsistent or unknown consistency Imprecise	Undetected for most; suspected for QOL measures	Fair to poor	Short study durations (1 to 12 weeks), small number of studies reporting the outcomes and too few events (for mortality and MVAs)	Referral population with known OSA

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Questionnaire/Tool (KQ 2), Test (KQ 3), Intervention (KQs 4, 5, 8), or Outcome (KQ 6)	No. of Studies and Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
	(90)						
Airway surgery	Mortality: 3 RCTs (127) QOL (SF-36 PCS, MCS): 2 RCTs (92) Sleep-related QOL: 1 RCT (60) Cognitive impairment: 1 RCT (60)	Mortality: No deaths in any study (12 weeks to 15 months) QOL (SF-36): No benefit found over 8 to 24 weeks Sleep-related QOL: No benefit measured on SAQLI; possible benefit with TCRFTA compared with sham surgery on FOSQ but not SNORE25 Cognitive impairment: No benefit on multiple measures of reaction time	Unknown Imprecise	Undetected	Good to fair	1 trial for each of 5 different surgeries (N=32 to 67); some study durations limited for assessing health outcomes; few total events	Potentially limited; OSA patients from ENT clinics, sleep clinics, or referrals; those deemed good candidates for surgery
Bariatric surgery	Mortality, QOL (SF-36), Headaches: 1 RCT with 2-year followup (60)	Mortality: No deaths QOL: SF-36 MCS score: -0.3 (95% CI, -5.3 to 4.8) SF-36 PCS score: 9.3 (95% CI, 0.5 to 18.0) Headache: 1 vs. 0 persons	Unknown consistency[¶] Imprecise	Undetected	Fair	Small numbers of total events (for mortality)	Potentially limited; morbidly obese candidates for bariatric surgery
Weight loss programs	Mortality: 4 RCTs (451) General QOL (SF-36 or 15D): 3 RCTs (150) EQ-5D-VAS: 1 RCT (60) Sleep-related QOL (FOSQ): 1 RCT (45) Cognitive impairment: 1 RCT (45)	Mortality: 1 total death over 9 to 208 weeks General QOL: No benefit in 1 RCT measured by the 15D; 2 trials provide ≥1 scores on individual SF-36 domains EQ-5D-VAS: No difference after 13 weeks of treatment, but greater improvement for the treatment group after 13 additional weeks of followup (between-group difference, 9 [95% CI, 2 to 16]) FOSQ: 1 RCT found no benefit Cognitive impairment: 1 RCT found no benefit on multiple measures of cognitive function at 12 weeks	Unknown Imprecise	Undetected	Good to fair	Small numbers of total events (for mortality); heterogeneity of reporting for QOL; single small study for some outcomes	Obese men and women, generally with moderate to severe OSA
KQ 6. Is there an association between AHI and health outcomes?							
All-cause mortality	6 prospective cohorts (11,003)[#]	For AHI ≥30 (severe OSA): HR, 2.07 (95% CI, 1.48 to 2.91)	Consistent Precise	Undetected	Good	Risk of residual confounding	General population
Cardiovascular mortality	2 prospective cohorts (3,173)	For AHI ≥30 (severe), adjusted HR, 2.87 (95% CI, 1.1 to 7.3) to 5.9 (95% CI, 2.6 to 13.3)	Consistent Imprecise	Undetected	Fair to good	Risk of residual confounding	General population

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Questionnaire/Tool (KQ 2), Test (KQ 3), Intervention (KQs 4, 5, 8), or Outcome (KQ 6)	No. of Studies and Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
Cancer-related mortality	1 prospective cohort (1,522)	For AHI ≥30: adjusted HR, 4.8 (95% CI, 1.7 to 13.2)	Unknown Imprecise	Undetected	Fair	Single study; risk of residual confounding; lack of precise information for some risk factors (e.g., smoking)	General population
Cardiovascular events	1 prospective cohort for each: nonfatal CV events (1,651) HF (4,422) CHD (4,422)	Nonfatal CV events for AHI ≥30: OR, 3.17 (95% CI, 1.12 to 7.52) Neither CHD nor incident HF were associated with OSA (of any severity) for men or for women in adjusted analyses**	Unknown Imprecise	Undetected	Fair to good	Single study for each outcome; potential measurement bias, risk of residual confounding	General population
Stroke	1 prospective cohort (5,422)	For men, AHI ≥19: adjusted HR, 2.86 (95% CI, 1.10 to 7.39) For women: HR, 1.21 (95% CI, 0.65 to 2.24)	Unknown Imprecise	Undetected	Fair to good	Single study; masking of outcomes assessors NR, risk of residual confounding	General population
Cognitive impairment or dementia	1 prospective cohort (298)	For AHI ≥15: adjusted OR, 1.85 (95% CI, 1.11 to 3.08)	Unknown Imprecise	Undetected	Fair	Single study, risk of residual confounding	Older women
Cognitive decline	1 prospective cohort (2,636)	For AHI ≥15: adjusted OR, 1.14 (95% CI, 0.84 to 1.54) on Trails B and OR, 0.99 (95% CI, 0.79 to 1.24) on 3MS	Unknown Imprecise	Undetected	Fair	Single study, risk of residual confounding	Older men
KQ 7. Are there harms associated with screening or diagnostic testing for OSA?							
No studies identified							
KQ 8. Are there harms associated with treatment of OSA?							
CPAP	9 RCTs (1,759)	Overall, 2% to 47% had specific adverse events while using CPAP. Commonly reported harms were oral or nasal dryness, eye or skin irritation, rash, epistaxis, and pain	Consistent Imprecise	Undetected	Fair	High heterogeneity in reporting and findings	Referral population with known OSA
Mandibular advancement devices	8 RCTs (443)	17% to 74% had any harms while using MADs. Common were oral or nasal dryness, excess salivation, oral mucosal/dental/jaw symptoms	Inconsistent Imprecise	Undetected	Fair	High amount of heterogeneity	Referral population with known OSA

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Questionnaire/Tool (KQ 2), Test (KQ 3), Intervention (KQs 4, 5, 8), or Outcome (KQ 6)	No. of Studies and Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
Airway surgery	4 RCTs (205)	1% to 81% of participants had harms from surgery. Most common were pain, postoperative bleeding, difficulty speaking and swallowing, change in vocal quality, hematomas, ulcerations, infections, temporary nasal regurgitation, and pain	Unknown Imprecise	Undetected	Fair	Small sample sizes; just 1 trial for each of 4 different surgeries	General population of patients with OSA deemed suitable for surgery
Bariatric surgery	1 RCT (60)	1 rehospitalization for additional surgery in treatment arm	Unknown Imprecise	Undetected	Fair	Single study with small sample	Morbidly obese
Weight loss, diet and exercise	1 RCT (63) of very low-calorie diet	Harms were reported by <10% of patients and included constipation, elevated alanine aminotransferase concentrations, dizziness, gout, and dry lips	Unknown Imprecise	Undetected	Fair	Single study with small sample	Obese men and women, generally with moderate to severe OSA

* This includes 24 studies (n=1,865) from the 2011 SR and 46 studies (n=5,008) from the 2007 Technology Assessment that were summarized by the 2011 SR.
† In this table, the total number of RCTs and participants reporting each outcome for CPAP or MADs are more than the number that contributed to the data in column 3 because we did not enter the CPAP or MAD "vs. control" data. Rather, we focused on the CPAP or MAD vs. sham data. We did, however, consider evidence from both comparator groupings in our assessments.
‡ Selected results for the most commonly reported outcomes are included in this table. Details on additional measures (e.g., Nottingham Health Profile) with few studies and insufficient evidence to draw conclusions are provided in the text and Appendixes.
§ TIA: few events across 3 RCTs (CPAP vs. comparators: total of 4 vs. 7 combining all trials); stroke: few events across 4 RCTs (CPAP vs. comparators: 3 vs. 3 combining all trials). Trial durations were 12 weeks, 24 weeks, 1 year, and 4 years (median followup).
‖ MI: few events across 5 RCTs (5 vs. 8 combining all trials); incident or unstable angina: few events across 4 RCTs (4 vs. 9 combining all trials); incident atrial fibrillation: 3 RCTs (12 vs. 20 events combined).
¶ For SF-36 PCS, improvement is consistent with that expected from a large weight loss.
# Two of the publications used data from the same cohort (WSCS) and we did not double-count those participants here (we just used one of the publications in the meta-analysis).
** For the subgroup of men age ≤70 years, participants with AHI ≥30 were more likely to develop CHD than those with AHI <5 (adjusted HR, 1.68 [95% CI, 1.02 to 2.76]).

Abbreviations: 3MS=Modified Mini-Mental State Examination; AHI=apnea hypopnea index; AUC=area under the curve; BP=blood pressure; CBV=cerebrovascular; CHD=coronary heart disease; CI=confidence interval; CPAP=continuous positive airway pressure; CV=cardiovascular; DBP=diastolic blood pressure; ENT=ear, nose, and throat (otolaryngology); ESS=Epworth Sleepiness Scale; EQ-5D=European Quality of Life Scale; FOSQ=Functional Outcomes of Sleep Questionnaire; HF=heart failure; HR=hazard ratio; KQ=key question; LAUP=laser-assisted uvulopalatoplasty; LR=likelihood ratio; MAD=mandibular advancement device; MCS=mental component summary score; MVA=motor vehicle accident; MVAP=Multivariable Apnea Prediction; N=number; NHP=Nottingham Health Profile; NR=not reported; OR=odds ratio; OSA=obstructive sleep apnea; OSAS=obstructive sleep apnea syndrome; PCS=physical component summary score; PSG=polysomnography; PM=portable monitor; QOL=quality of life; RCT=randomized, controlled trial; SAQLI=Sleep Apnea Quality of Life Index; SBP=systolic blood pressure; SF-36=Medical Outcome Short-Form (36-Item) Health Survey; Sn=sensitivity; Sp=specificity; SR=systematic review; TIA=transient ischemic attack; UPPP=uvulopalatopharyngoplasty; WMD=weighted mean difference; WSCS=Wisconsin Sleep Cohort Study.

Prevalence

Reported estimates of the prevalence vary, likely because of variation in the definitions of obstructive sleep apnea (OSA) used (i.e., different apnea-hypopnea index [AHI] cutoffs), sampling biases, year of publication, or combinations of these factors.[31] A recent systematic review estimated a prevalence range of 2 to 14 percent among four community-based studies[8] after correcting for oversampling. Pooled estimates from the systematic review indicated a prevalence of 6 percent (95% confidence interval [CI], 3.7 to 8.3) for an AHI threshold of 15 and a prevalence of 14 percent (95% CI, 8.3 to 20) for an AHI threshold of 5. Sample sizes of the four included studies ranged from 360 to 1,741. Two of the four studies were conducted in the United States;[15,32] the others were conducted in India and Norway. For the largest U.S.-based study (N=1,741),[32] the estimated prevalence was 3.8 percent (95% CI, 2.9 to 9.8) using an AHI threshold of 15. The prevalence was higher among the subsample with obesity (almost 10%), was higher for men than women (6.6% vs. 1.8%), and increased with age (0.7% for ages 20 to 44, 5.6% for ages 45 to 64, and 8% for ages 65 to 100). For the other U.S.-based study (N=602, Wisconsin Sleep Cohort Study[15] data published in 1993), the estimated prevalence was 6.5 percent (95% CI, 4.5 to 8.5) using an AHI threshold of 15 and 17 percent (95% CI, 14 to 21) using an AHI threshold of 5. The prevalence was higher for men than women (9.1% vs. 4.0% using an AHI threshold of 15 and 24% vs. 9% using an AHI threshold of 5). From the same study, the estimated prevalence for an OSA syndrome (AHI of at least 5 plus excessive daytime sleepiness) was 4 percent for men (95% CI, 2 to 6) and 2 percent for women (95% CI, 0.3 to 3.7).

We searched for estimates of how many people with mild, moderate, or severe OSA would be detected by screening, and we were only able to find some of the information. Specifically, estimates for those with mild OSA (AHI of at least 5 but <15) and those with moderate/severe (combining the two categories, with AHI of at least 15) are available. The systematic review described in the previous paragraph[8] indicated that 8 percent of the population would have mild OSA and that 6 percent would have moderate or severe OSA. The two U.S.-based studies that were included found about 10 percent[15] with mild OSA and 3.8[32] to 6.5[15] percent with moderate or severe OSA when using data from the 1990s; long-term followup from one of them estimated a 16 percent prevalence for mild OSA and 10 percent for moderate or severe OSA.[33]

Longitudinal epidemiological studies and modeling studies estimate that the prevalence of OSA is increasing, perhaps due to rising rates of obesity.[33,34] Recent publications use data from the Wisconsin Sleep Cohort Study and statistical modeling to estimate current OSA prevalence. This approach found that the prevalence of OSA has increased over the last two decades.[33] Data published in 2009 (N=1,500) and 2013 (N=1,520) reported a prevalence around 20 to 30 percent for men and 10 to 15 percent for women ages 30 to 70 years when using an AHI threshold of 5.[33,34] When more stringent definitions are used, either combining an AHI of at least 5 with report of at least one symptom of disturbed sleep or using an AHI threshold of 15, the estimated prevalence was approximately 15 percent in men and 5 percent in women.[33,34]

Multiple cohort studies have found that OSA is approximately 2 to 3 times more common in men than women, although the gap narrows at the age of menopause in women.[15-17,35] The prevalence of OSA appears to increase with age through the sixth to seventh decade and then plateaus.[14,16,17] In both males and females, multiple epidemiological studies have found that the prevalence of OSA progressively increases as body mass index (BMI) increases. Using data from the Wisconsin Sleep Cohort Study, a prospective study of nearly 700 adults with 4-year longitudinal

followup, the authors reported that a 10 percent increase in weight was associated with a six-fold increase in risk of incident OSA.[7] In another study that used age- and BMI-specific OSA prevalence data from the Wisconsin Sleep Cohort Study combined with BMI population distributions from the U.S. National Health and Nutrition Examination Survey database, the estimated prevalence of OSA increased from 1990 to 2010 in every age group and BMI category studied, in some cases by as much as 50 percent.[33] It is unclear whether the prevalence of OSA differs by race or ethnicity; most population-based studies in the United States have been conducted in select populations and have not sought to describe this relationship.[31,277]

Burden

Patients with untreated, severe OSA have an increased risk of all-cause mortality. A 2011 comparative effectiveness review for the Agency for Healthcare Research and Quality (AHRQ) found high strength of evidence from four studies indicating that an AHI greater than 30 is an independent predictor of all-cause mortality.[1] The review found two studies with some evidence of an association between AHI and incident diabetes but concluded that the association may be confounded by obesity, which may result in both OSA and diabetes.[1] The authors concluded that evidence was insufficient for the association between AHI and other clinical outcomes.[1]

OSA has been associated with a wide range of other adverse health outcomes in various publications. However, there is some controversy in the literature regarding the extent to which OSA directly contributes to various adverse outcomes—above and beyond the contributions of age, BMI, and other potential confounders. One systematic review from the 1990s (including 54 epidemiological studies) examined the association between sleep apnea and health-related outcomes and concluded that most studies were poorly designed and found only weak or contradictory evidence for an association with cardiac arrhythmias, ischemic heart disease, cardiac failure, systemic or pulmonary hypertension, and stroke.[278] In a systematic review of case-control and matched cohort studies, drivers with OSA had an increased risk of motor vehicle accidents (relative risk, 2.43; 95% CI, 1.21 to 4.89).[279] However, the authors noted that most included studies were rated as low quality because of retrospective design, lack of adjustment for important confounders, and self-reported outcome or lack of independent outcome assessment and that there was significant statistical heterogeneity in results.[279] Two recent systematic reviews of cohort studies found that people with OSA have increased risk of stroke, but the relationship between OSA and risk of ischemic heart disease is uncertain.[280,281]

Appendix A Table 1. Summary of Guidelines From Other Groups

Group, Year	Screening or Treatment?	Recommendations
American College of Physicians (ACP), 2013[76]	Treatment	All overweight and obese patients diagnosed with OSA should be encouraged to lose weight. (strong recommendation; low-quality evidence) CPAP treatment as initial therapy for patients diagnosed with OSA. (strong recommendation; moderate-quality evidence) Mandibular advancement devices as an alternative therapy to CPAP treatment for patients diagnosed with OSA who prefer mandibular advancement devices or for those with adverse effects associated with CPAP treatment. (weak recommendation; low-quality evidence)
American Academy of Sleep Medicine (AASM), 2009[282]	Screening	Routine health maintenance evaluations should include questions about OSA (e.g., history of snoring and daytime sleepiness), as well as an evaluation for the presence of obesity, retrognathia, and hypertension. Positive findings should trigger a comprehensive sleep evaluation. The diagnostic strategy includes a sleep-oriented history and physical examination, objective testing, and education of the patient. The presence or absence and severity of OSA must be determined before initiating treatment to identify those patients at risk of developing the complications of sleep apnea, guide selection of appropriate treatment, and provide a baseline to establish the effectiveness of subsequent treatment.
	Treatment	Once the diagnosis is established, the patient should be included in deciding an appropriate treatment strategy that may include CPAP devices, oral appliances, behavioral treatments, surgery, and adjunctive treatments. OSA should be approached as a chronic disease requiring long-term, multidisciplinary management.
Institute for Clinical Systems Improvement (ICSI), 2008[283]	Screening	Appropriately sensitive overnight oximetry (when combined with history and physical) can be a useful tool in screening patients with a high pretest probability of OSA and excluding patients with a low pretest probability of OSA. (Conclusion Grade II) Unattended sleep studies can be valuable tools in the diagnosis of OSA, providing an accurate and reliable AHI in patients with a high pretest probability, but they carry the following limitations: absence of trained technician means no one can enlist patient cooperation, they cannot make continuous patient observations, they cannot intervene for the medically unstable patient, and they cannot provide therapeutic intervention (i.e., CPAP, oxygen, supine positioning, resuscitation). (Conclusion Grade III)
National Institute for Health and Clinical Excellence (NICE), 2008[284]	Screening	Moderate to severe obstructive sleep apnea hypopnea syndrome (OSAHS) can be diagnosed from patient history and a sleep study using oximetry or other monitoring devices carried out in the person's home. In some cases, further studies that monitor additional physiological variables in a sleep laboratory or at home may be required, especially when alternative diagnoses are being considered.
	Treatment	CPAP is recommended as a treatment option for adults with moderate or severe symptomatic OSAHS. CPAP is only recommended as a treatment option for adults with mild OSAHS if: • they have symptoms that affect their quality of life and ability to go about their daily activities, and • lifestyle advice and any other relevant treatment options have been unsuccessful or are considered inappropriate. The diagnosis and treatment of OSAHS, and the monitoring of the response, should be carried out by a specialist service with appropriately trained medical and support staff.

Abbreviations: AASM=American Academy of Sleep Medicine; ACP=American College of Physicians; AHI=apnea-hypopnea index; CPAP=continuous positive airway pressure; ICSI=Institute for Clinical Systems Improvement; NICE=National Institute for Health and Clinical Excellence; OSA=obstructive sleep apnea; OSAHS=obstructive sleep apnea-hypopnea syndrome.

Original Search Strategies

PubMed intervention/treatment search, 9/30/2014

Search	Query	Items Found
#1	Search ("Sleep Apnea Syndromes"[MeSH] OR "Sleep Apnea, Obstructive"[MeSH] OR "Obstructive Sleep Apneas"[tw] OR "Obstructive Sleep Apnea"[tw] OR "Obstructive Sleep Apnea Syndrome"[tw] OR "Obstructive Sleep Apnoeas"[tw] OR "Obstructive Sleep Apnoea"[tw] OR OSAHS[tw] OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"[tw])	28401
#2	Search "Positive-Pressure Respiration"[Mesh:NoExp]	14880
#3	Search "Continuous Positive Airway Pressure"[Mesh]	3985
#4	Search ("Continuous Positive Airway Pressure"[tw] OR CPAP[tw])	9222
#5	Search "Intermittent Positive-Pressure Ventilation"[MeSH]	2004
#6	Search ("Intermittent Positive Pressure Ventilation"[tw] OR "IPPV"[tw] OR "Inspiratory Positive-Pressure Ventilation"[tw] OR "Inspiratory Positive Pressure Ventilation"[tw] OR "Biphasic Intermittent Positive Airway Pressure"[tw] OR BiPAP[tw])	3260
#7	Search "Mandibular Prosthesis"[MeSH Terms]	798
#8	Search ("mandibular advancement device"[tw] OR "mandibular advancement devices"[tw])	180
#9	Search "Mandibular Advancement/instrumentation"[Mesh]	516
#10	Search ("oral appliance"[tw] OR "oral appliances"[tw])	641
#11	Search ("General Surgery"[MeSH] OR "general surgery"[tw])	39479
#12	Search ("otolaryngology"[MeSH] OR "otolaryngology"[tw] OR "Otorhinolaryngology"[tw] OR "Laryngology"[tw])	17942
#13	Search ("surgery, plastic"[MeSH] OR "Plastic Surgery"[tw])	29779
#14	Search ("Surgical Procedures, Operative"[MeSH] OR "Operative Surgical Procedure"[tw] OR "Operative Surgical Procedures"[tw] OR "Operative Procedures"[tw] OR "Operative Procedure"[tw])	2394551
#15	Search "Bariatric Surgery"[Mesh]	14577
#16	Search (UPPP[tw] OR uvulopalatopharyngoplasty[tw])	921
#17	Search (septoplasty[tw] AND "turbinate reduction"[tw])	39
#18	Search ("Pillar Procedure"[tw] OR "soft palate implants"[tw])	0
#19	Search "Hyoid advancement"[tw]	11
#20	Search "Orthognathic Surgical Procedures"[Mesh]	1136
#21	Search "Osteotomy, Le Fort"[Mesh]	1482
#22	Search "Osteotomy, Sagittal Split Ramus"[Mesh]	284
#23	Search ("tonsillectomy"[MeSH] OR tonsillectomy[tw])	9651
#24	Search ("Exercise Therapy"[MeSH] OR exercise[MeSH] OR "exercise therapy"[tw] OR "exercise therapies"[tw])	142239
#25	Search ("weight loss"[MeSH] OR "weight loss"[tw] OR "weight reduction"[tw])	72130
#26	Search ("Body Mass Index"[Mesh] OR "body mass index"[tw] OR BMI[tw])	164639
#27	Search ("Obesity"[Mesh] OR obesity[tw])	201780
#28	Search "Diet, Reducing"[Mesh]	9355
#29	Search (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28)	2904782
#30	Search (#1 and #29)	15311
#31	Search ((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	579517
#32	Search (#30 and #31)	1051
#33	Search (#30 and #31) Filters: Humans	1007
#34	Search (#30 and #31) Filters: Humans; Adult: 19+ years	862
#35	Search (#30 and #31) Filters: Publication date from 2010/01/01; Humans; Adult: 19+ years	301
#36	Search (#30 and #31) Filters: Publication date from 2010/01/01; Humans; English; Adult: 19+ years	290
#37	Search (#35 not #36)	11
#38	Search ("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields]))	1664863
#39	Search (#30 and #38)	4240
#40	Search (#30 and #38) Filters: Humans	4211

Appendix B1. Detailed Methods

Search	Query	Items Found
#41	Search (#30 and #38) Filters: Humans; Adult: 19+ years	3247
#42	Search (#30 and #38) Filters: Publication date from 2010/01/01; Humans; Adult: 19+ years	1256
#43	Search (#30 and #38) Filters: Publication date from 2010/01/01; Humans; English; Adult: 19+ years	1182
#44	Search (#42 not #43)	74

PubMed screening search, 9/29/2014

Search	Query	Items Found
#1	Search ("Sleep Apnea Syndromes"[MeSH] OR "Sleep Apnea, Obstructive"[MeSH] OR "Obstructive Sleep Apneas"[tw] OR "Obstructive Sleep Apnea"[tw] OR "Obstructive Sleep Apnea Syndrome"[tw] OR "Obstructive Sleep Apnoeas"[tw] OR "Obstructive Sleep Apnoea"[tw] OR OSAHS[tw] OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"[tw])	28390
#2	Search "Questionnaires"[Mesh]	309519
#3	Search "Epworth Sleepiness Scale"[All Fields]	2137
#4	Search "STOP Questionnaire"[All Fields]	21
#5	Search "STOP-Bang Questionnaire"[All Fields]	41
#6	Search "Berlin Questionnaire"[All Fields]	250
#7	Search "Wisconsin Sleep Questionnaire"[All Fields]	3
#8	Search "Decision Support Techniques"[Mesh]	60053
#9	Search ("Clinical prediction tool" OR "Clinical prediction rule" OR "Clinical prediction score")	497
#10	Search "Multivariable Apnea Prediction Index"[All Fields]	9
#11	Search "Multivariable Apnoea Prediction Index"[All Fields]	0
#12	Search "Snoring Scale"[All Fields]	22
#13	Search "NAMES"[All Fields]	14085
#14	Search "Sleep Apnea Clinical Score"[All Fields]	10
#15	Search "Neck circumference"[All Fields]	621
#16	Search Mallampati[All Fields]	511
#17	Search "Craniofacial structure"[All Fields]	121
#18	Search "Nocturnal choking"[All Fields]	21
#19	Search "Nocturnal gasping"[All Fields]	3
#21	Search ("Body Mass Index"[Mesh]) OR "Body Weight"[Mesh] OR "Obesity"[Mesh])	386293
#22	Search ("Snoring"[Mesh] OR snoring)	5547
#23	Search Sleepiness	30048
#24	Search (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #21 or #22 or #23)	782859
#25	Search (#1 and #24)	12584
#26	Search ("Mass Screening"[Mesh] OR screening[tiab])	378755
#27	Search "Predictive Value of Tests"[Mesh]	142093
#28	Search ("Diagnostic Tests, Routine"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "ROC Curve"[Mesh] OR "Diagnosis"[Mesh] OR "Reproducibility of Results"[Mesh] OR "False Negative Reactions"[Mesh] OR "False Positive Reactions"[Mesh] OR "predictive value"[tw] OR sensitivity[tw] OR specificity[tw] OR accuracy[tw] OR screen[tw] OR diagno*[tw] OR ROC[tw] OR reproducib*[tw] OR "false positive"[tw] OR "false negative"[tw] OR "likelihood ratio"[tw])	8792662
#29	Search (#26 or #27 or #28)	8900912
#30	Search (#25 and #29)	10585
#31	Search (Autobiography[Publication Type] OR Bibliography[Publication Type] OR Biography[Publication Type] OR Case Reports[Publication Type] OR Classical Article[Publication Type] OR comment[Publication Type] OR Congresses[Publication Type] OR Consensus Development Conference[Publication Type] OR Dictionary[Publication Type] OR Directory[Publication Type] OR Editorial[Publication Type] OR Electronic supplementary materials[Publication Type] OR Festschrift[Publication Type] OR In Vitro[Publication Type] OR Interactive Tutorial[Publication Type] OR Interview[Publication Type] OR Lectures[Publication Type] OR Legal Cases[Publication Type] OR Legislation[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Newspaper article[Publication Type] OR Patient Education Handout[Publication Type] OR Personal Narratives[Publication Type]	3692864

Appendix B1. Detailed Methods

Search	Query	Items Found
	OR Periodical Index[Publication Type] OR Pictorial works[Publication Type] OR Popular works[Publication Type] OR Portraits[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type] OR Webcasts[Publication Type])	
#32	Search (#30 not #31)	9359
#33	Search (#30 not #31) Filters: Adult: 19+ years	6029
#34	Search (#30 not #31) Filters: Humans; Adult: 19+ years	6029
#35	Search (#30 not #31) Filters: Humans; English; Adult: 19+ years	5279
#36	Search (#34 NOT #35)	750

PubMed KQ6 search, 9/29/2014

Search	Query	Items Found
#1	Search ("Sleep Apnea Syndromes"[MeSH] OR "Sleep Apnea, Obstructive"[MeSH] OR "Obstructive Sleep Apneas"[tw] OR "Obstructive Sleep Apnea"[tw] OR "Obstructive Sleep Apnea Syndrome"[tw] OR "Obstructive Sleep Apnoeas"[tw] OR "Obstructive Sleep Apnoea"[tw] OR OSAHS[tw] OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"[tw])	28401
#2	Search ("Apnea hypopnea Index"[All Fields] OR "Apnea/hypopnea index"[All Fields] OR "Apnoea hypopnea index"[All Fields] OR "Apnoea hypopnoea index"[All Fields] OR "Apnoea/hypopnoea index"[All Fields])	4725
#3	Search (#1 and #2)	4573
#4	Search ("Patient Outcome Assessment"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Fatal Outcome"[Mesh])	749768
#5	Search outcome*[tiab]	961492
#6	Search ("Mortality"[Mesh] OR "mortality" [Subheading] OR mortality[tiab])	864162
#7	Search ("Quality of Life"[Mesh] OR "quality of life"[tiab])	195341
#8	Search ("Motor Vehicles"[Mesh] OR "motor vehicle"[tiab] OR "motor vehicles"[tiab])	24728
#9	Search ("Cardiovascular Diseases"[Mesh]) OR "Myocardial Infarction"[Mesh] OR cardiovascular*[tiab])	2008239
#10	Search ("Stroke"[Mesh]) OR "Cerebrovascular Disorders"[Mesh] OR stroke[tiab] OR cerebrovasc*[tiab])	361286
#11	Search "heart failure"[tiab]	110169
#12	Search ("Headache"[Mesh] OR headache[tiab])	61110
#13	Search ("Mild Cognitive Impairment"[Mesh]) OR "Cognition Disorders"[Mesh] OR cognit*[tiab])	247674
#14	Search (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)	4056320
#15	Search (#3 and #14)	2370
#16	Search (Autobiography[Publication Type] OR Bibliography[Publication Type] OR Biography[Publication Type] OR Case Reports[Publication Type] OR Classical Article[Publication Type] OR comment[Publication Type] OR Congresses[Publication Type] OR Consensus Development Conference[Publication Type] OR Dictionary[Publication Type] OR Directory[Publication Type] OR Editorial[Publication Type] OR Electronic supplementary materials[Publication Type] OR Festschrift[Publication Type] OR In Vitro[Publication Type] OR Interactive Tutorial[Publication Type] OR Interview[Publication Type] OR Lectures[Publication Type] OR Legal Cases[Publication Type] OR Legislation[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Newspaper article[Publication Type] OR Patient Education Handout[Publication Type] OR Personal Narratives[Publication Type] OR Periodical Index[Publication Type] OR Pictorial works[Publication Type] OR Popular works[Publication Type] OR Portraits[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type] OR Webcasts[Publication Type] OR Twin Studies[Publication Type])	3694043
#17	Search (#15 not #16)	2327
#18	Search (#15 not #16) Filters: Adult: 19+ years	1826
#19	Search (#15 not #16) Filters: Humans; Adult: 19+ years	1826
#20	Search (#15 not #16) Filters: Publication date from 2010/01/01; Humans; Adult: 19+ years	781
#21	Search (#15 not #16) Filters: Publication date from 2010/01/01; Humans; English; Adult: 19+ years	743
#22	Search (#20 not #21)	38

Appendix B1. Detailed Methods

PubMed Diagnosis Search, 9-29-14

Search	Query	Items Found
#1	Search ("Sleep Apnea Syndromes"[MeSH] OR "Sleep Apnea, Obstructive"[MeSH] OR "Obstructive Sleep Apneas"[tw] OR "Obstructive Sleep Apnea"[tw] OR "Obstructive Sleep Apnea Syndrome"[tw] OR "Obstructive Sleep Apnoeas"[tw] OR "Obstructive Sleep Apnoea"[tw] OR OSAHS[tw] OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"[tw]))	28390
#2	Search "Sleep Apnea Syndromes/diagnosis"[Majr]	4408
#3	Search "Sleep Apnea, Obstructive/diagnosis"[Majr]	2256
#4	Search "Monitoring, Ambulatory/instrumentation"[Majr]	2980
#5	Search (Polysomnography[Mesh] OR Polysomnographies[tw])	14079
#6	Search (oximetry[MeSH] OR oximetry[tw] OR "Oximetries"[tw])	14957
#7	Search "Diagnostic Tests, Routine"[Mesh]	7019
#8	Search "sleep monitoring"[All Fields]	245
#9	Search PSG	3498
#10	Search polygraphy	496
#11	Search Actigraphy	2620
#12	Search Apnoescreen	4
#13	Search ((home AND monitor*))	13099
#14	Search Monitoring system*	8700
#15	Search "portable respiratory monitoring"	4
#16	Search Portable monitor*	308
#17	Search ("diagnosis"[MeSH] OR "diagnosis"[tw] OR "diagnoses"[tw] OR "Reproducibility of Results"[MeSH] OR "Reproducibility of Results"[tw] OR "Reproducibility of Findings"[tw] OR "Predictive Value of Tests"[Mesh] OR "Predictive Value"[tw] OR "ROC Curve"[Mesh] OR "ROC"[tw] OR "Validity of Results"[tw] OR reliab*[tw] OR valid*[tw] OR "False Negative Reactions"[MeSH] OR "false negative"[tw] OR "False Positive Reactions"[MeSH] OR "false positive"[tw] OR "accuracy"[tw] OR reproducib*[tw] OR "likelihood ratio"[tw] OR "accuracy"[tw] OR "sensitivity"[tw] OR "specificity"[tw])	8743832
#18	Search (#1 AND (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17))	20457
#19	Search (#1 AND (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17)) Filters: Humans	19169
#20	Search (#1 AND (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17)) Filters: Publication date from 2010/01/01; Humans	5426
#21	Search (Autobiography[Publication Type] OR Bibliography[Publication Type] OR Biography[Publication Type] OR Case Reports[Publication Type] OR Classical Article[Publication Type] OR comment[Publication Type] OR Congresses[Publication Type] OR Consensus Development Conference[Publication Type] OR Dictionary[Publication Type] OR Directory[Publication Type] OR Editorial[Publication Type] OR Electronic supplementary materials[Publication Type] OR Festschrift[Publication Type] OR In Vitro[Publication Type] OR Interactive Tutorial[Publication Type] OR Interview[Publication Type] OR Lectures[Publication Type] OR Legal Cases[Publication Type] OR Legislation[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Newspaper article[Publication Type] OR Patient Education Handout[Publication Type] OR Personal Narratives[Publication Type] OR Periodical Index[Publication Type] OR Pictorial works[Publication Type] OR Popular works[Publication Type] OR Portraits[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type] OR Webcasts[Publication Type])	3692864
#22	Search (#20 NOT #21)	4647
#23	Search (#20 NOT #21) Filters: Adult: 19+ years	3035
#24	Search (#20 NOT #21) Filters: English; Adult: 19+ years	2806
#25	Search (#23 NOT #24)	229

Appendix B1. Detailed Methods

Cochrane Interventions/Treatment search, 9-30-14

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] or [mh "Sleep Apnea, Obstructive"] or [mh "Obstructive Sleep Apneas"] or [mh "Obstructive Sleep Apnea"] or [mh "Obstructive Sleep Apnea Syndrome"] or "Obstructive Sleep Apnoeas" or "Obstructive Sleep Apnoea" or OSAHS or ("sleep apnea" and hypopnea) or "sleep disordered breathing"	1966
#2	[mh ^"Positive-Pressure Respiration"]	1249
#3	[mh "Continuous Positive Airway Pressure"]	650
#4	"Continuous Positive Airway Pressure" or CPAP	2344
#5	[mh "Intermittent Positive-Pressure Ventilation"]	194
#6	"Intermittent Positive Pressure Ventilation" or "IPPV" or "Inspiratory Positive-Pressure Ventilation" or "Inspiratory Positive Pressure Ventilation" or "Biphasic Intermittent Positive Airway Pressure" or BiPAP	592
#7	[mh "Mandibular Prosthesis"]	6
#8	"mandibular advancement device" or "mandibular advancement devices"	46
#9	[mh "Mandibular Advancement"]	125
#10	[mh "General Surgery"] or "general surgery"	2042
#11	[mh otolaryngology] or otolaryngology or Otorhinolaryngology or Laryngology	5993
#12	[mh "Surgery, Plastic"] or "Plastic Surgery"	1236
#13	[mh "Surgical Procedures, Operative"] or "Operative Surgical Procedure" or "Operative Surgical Procedures" or "Operative Procedures" or "Operative Procedure"	99826
#14	[mh "Bariatric Surgery"]	764
#15	UPPP or uvulopalatopharyngoplasty	103
#16	(septoplasty and "turbinate reduction")	3
#17	"Pillar Procedure" or "soft palate implants"	1
#18	"Hyoid advancement"	0
#19	[mh "Orthognathic Surgical Procedures"]	61
#20	[mh "Osteotomy, Le Fort"]	63
#21	[mh "Osteotomy, Sagittal Split Ramus"]	14
#22	[mh tonsillectomy] or tonsillectomy	1716
#23	[mh "Exercise Therapy"] or [mh exercise] or "exercise therapy" or "exercise therapies"	19323
#24	[mh "weight loss"] or "weight loss" or "weight reduction"	8842
#25	[mh "Body Mass Index"] or "body mass index" or BMI	17317
#26	[mh Obesity] or obesity	13520
#27	[mh "Diet, Reducing"]	1581
#28	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27	149515
#29	#1 and #28	1362

Cochrane Screening search, 9-30-14

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] or [mh "Sleep Apnea, Obstructive"] or [mh "Obstructive Sleep Apneas"] or [mh "Obstructive Sleep Apnea"] or [mh "Obstructive Sleep Apnea Syndrome"] or "Obstructive Sleep Apnoeas" or "Obstructive Sleep Apnoea" or OSAHS or ("sleep apnea" and hypopnea) or "sleep disordered breathing"	1966
#2	[mh Questionnaires]	17241
#3	"Epworth Sleepiness Scale"	420
#4	"STOP Questionnaire"	2
#5	"STOP-Bang Questionnaire"	2
#6	"Berlin Questionnaire"	13
#7	"Wisconsin Sleep Questionnaire"	0
#8	[mh "Decision Support Techniques"]	3166
#9	"Clinical prediction tool" or "Clinical prediction rule" or "Clinical prediction score"	73
#10	"Multivariable Apnea Prediction Index"	0
#11	"Multivariable Apnoea Prediction Index"	0
#12	"Snoring Scale"	4
#13	"NAMES"	1745
#14	"Sleep Apnea Clinical Score"	2
#15	"Neck circumference"	40
#16	Mallampati	111

Appendix B1. Detailed Methods

ID	Search	Hits
#17	"Craniofacial structure"	2
#18	"Nocturnal choking"	1
#19	"Nocturnal gasping"	1
#20	[mh "Body Mass Index"] or [mh "Body Weight"] or [mh Obesity]	19124
#21	[mh Snoring] or snoring	419
#22	Sleepiness	1768
#23	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #21 or #22	23969
#24	#1 and #23	664
#25	[mh "Mass Screening"] or screening	28803
#26	[mh "Predictive Value of Tests"]	6169
#27	[mh "Diagnostic Tests, Routine"] or [mh "Sensitivity and Specificity"] or [mh "Predictive Value of Tests"] or [mh "ROC Curve"] or [mh Diagnosis] or [mh "Reproducibility of Results"] or [mh "False Negative Reactions"] or [mh "False Positive Reactions"] or "predictive value" or sensitivity or specificity or accuracy or screen* or diagno* or ROC or reproducib* or "false positive" or "false negative" or "likelihood ratio"	331387
#28	#25 or #26 or #27	331467
#29	#24 and #28 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials and Technology Assessments	529

Cochrane KQ6 search, 10-01-14

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] or [mh "Sleep Apnea, Obstructive"] or [mh "Obstructive Sleep Apneas"] or [mh "Obstructive Sleep Apnea"] or [mh "Obstructive Sleep Apnea Syndrome"] or "Obstructive Sleep Apnoeas" or "Obstructive Sleep Apnoea" or OSAHS or ("sleep apnea" and hypopnea) or "sleep disordered breathing"	1986
#2	"Apnea hypopnea Index" or "Apnea/hypopnea index" or "Apnoea hypopnea index" or "Apnoea hypopnoea index" or "Apnoea/hypopnoea index"	654
#3	#1 and #2	607
#4	[mh "Patient Outcome Assessment"] or [mh "Outcome Assessment (Health Care)"] or [mh "Fatal Outcome"]	99822
#5	outcome*	208437
#6	[mh Mortality] or mortality	50240
#7	[mh "Quality of Life"] or "quality of life"	37654
#8	[mh "Motor Vehicles"] or "motor vehicle" or "motor vehicles"	620
#9	[mh "Cardiovascular Diseases"] or [mh "Myocardial Infarction"] or cardiovascular*	97515
#10	[mh Stroke] or [mh "Cerebrovascular Disorders"] or stroke or cerebrovasc*	41189
#11	"heart failure"	12771
#12	[mh Headache] or headache	14079
#13	[mh "Mild Cognitive Impairment"] or [mh "Cognition Disorders"] or cognit*	31052
#14	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	340683
#15	#3 and #14 Publication Year from 2010 to 2014, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials and Technology Assessments	177

Cochrane Diagnosis search, 10-01-14

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] or [mh "Sleep Apnea, Obstructive"] or [mh "Obstructive Sleep Apneas"] or [mh "Obstructive Sleep Apnea"] or [mh "Obstructive Sleep Apnea Syndrome"] or "Obstructive Sleep Apnoeas" or "Obstructive Sleep Apnoea" or OSAHS or ("sleep apnea" and hypopnea) or "sleep disordered breathing"	1986
#2	[mh ^"Monitoring, Ambulatory"/IS]	125
#3	[mh Polysomnography] or Polysomnographies	1330
#4	[mh oximetry] or oximetry or Oximetries	1696
#5	[mh "Diagnostic Tests, Routine"]	311
#6	"sleep monitoring"	27
#7	PSG	384
#8	polygraphy	42
#9	Actigraphy	387
#10	Apnoescreen	1

#11	home and monitor*	3144
#12	Monitoring system*	11395
#13	"portable respiratory monitoring"	3
#14	Portable monitor*	375
#15	[mh diagnosis] or diagnosis or diagnoses or [mh "Reproducibility of Results"] or "Reproducibility of Results" or "Reproducibility of Findings" or [mh "Predictive Value of Tests"] or "Predictive Value" or [mh "ROC Curve"] or ROC or "Validity of Results" or reliab* or valid* or [mh "False Negative Reactions"] or "false negative" or [mh "False Positive Reactions"] or "false positive" or accuracy or reproducib* or "likelihood ratio" or "accuracy" or "sensitivity" or "specificity"	334889
#16	#1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)	1391
#17	#16 Publication Year from 2010 to 2014, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials and Technology Assessments	479

EMBASE Intervention Search, 10-6-14

No.	Query	Results
#43	#41 NOT #37	5
#42	#40 NOT #36	137
#41	#39 NOT #40	6
#40	#33 AND #38 AND [english]/lim	272
#39	#33 AND #38	278
#38	'cohort analysis'/exp OR 'epidemiological study' OR (cohort AND (study OR studies)) OR 'prospective study'/exp OR (prospective* AND cohort)	624,021
#37	#35 NOT #36	6
#36	#35 AND [english]/lim	562
#35	#33 AND #34	568
#34	'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'random allocation'/exp OR 'controlled trial'/exp OR 'control trial' OR ('control':ab,ti OR 'controlled':ab,ti AND 'trial':ab,ti)	4,685,658
#33	#4 AND #29 AND [humans]/lim AND [2010-2014]/py AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	1,448
#32	#4 AND #29 AND [humans]/lim AND [2010-2014]/py	4,392
#30	#4 AND #29	9,611
#29	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #15 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #28	176,391
#28	'weight reduction'/exp	103,035
#25	'tonsillectomy'/exp	11,569
#24	'sagittal split ramal osteotomy'/exp	165
#23	'maxilla osteotomy'/exp	2,083
#22	'orthognathic surgery'/exp	1,621
#21	'hyoid advancement'	20
#20	'pillar procedure' OR 'soft palate implants'	8
#19	'nose septum reconstruction'/exp AND 'turbinate reduction'	38
#18	'uvulopalatopharyngoplasty'/exp	1,194
#17	'bariatric surgery'/exp	19,692
#15	'otorhinolaryngology'/exp	19,509
#13	'general surgery'/exp	8,891
#12	'mandible reconstruction'/exp	3,870
#11	'mandibular advancement device' OR 'mandibular advancement devices'	254
#10	'mandible prosthesis'/exp	656
#9	'intermittent positive pressure ventilation' OR 'ippv' OR 'inspiratory positive-pressure ventilation' OR 'inspiratory positive pressure ventilation' OR 'biphasic intermittent positive airway pressure' OR bipap	4,895
#8	'intermittent positive pressure ventilation'/exp	2,792
#7	'positive end expiratory pressure'/exp/mj	11,754
#6	'cpap device'/exp	151
#5	'positive end expiratory pressure'/exp/mj	11,754
#4	#1 OR #2 OR #3	43,859
#3	'sleep apnea' AND hypopnea	7,727
#2	'obstructive sleep apnoeas' OR 'obstructive sleep apnoea'	4,530
#1	'sleep disordered breathing'/exp	43,459

EMBASE screening search, 10-07-14

No.	Query	Results
#21	#19 NOT #20	32
#20	#16 NOT #17 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim AND [english]/lim	318
#19	#16 NOT #17 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim	350
#18	#16 NOT #17	596
#17	#8 AND #15 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim)	706
#16	#8 AND #15	1,302
#15	#9 OR #10 OR #11 OR #12 OR #13 OR #14	5,021,470
#14	'diagnosis'/exp	4,846,516
#13	'receiver operating characteristic'/exp	48,005
#12	'sensitivity and specificity'/exp	201,366
#11	'diagnostic test'/exp	721,811
#10	'predictive value'/exp	58,047
#9	'mass screening'/exp	159,522
#8	#4 AND #7	3,876
#7	#5 OR #6	412,992
#6	'clinical prediction tool' OR 'clinical prediction rule' OR 'clinical prediction score'	740
#5	'questionnaire'/exp	412,296
#4	#1 OR #2 OR #3	44,485
#3	'sleep apnea' AND hypopnea	7,733
#2	'obstructive sleep apnoeas' OR 'obstructive sleep apnoea'	4,530
#1	'sleep disordered breathing'/exp OR 'sleep disordered breathing'	44,124

Gray Literature Searches, June 18-24, 2015

ClinicalTrials.gov Expert Searches (484 in EndNote):
SCREENING AND DIAGNOSIS (on 6/12 yield was N=303. On 6/18 increased to **304)**
INFLECT EXACT ("Adult" OR "Senior") [AGE-GROUP] AND (Ambulatory monitoring OR Polysomnograph* OR oximetr* OR diagnos* OR sleep monitoring OR PSG OR polygraphy OR Actigraphy OR Apnoescreen OR home monitor* OR Monitoring system* OR portable respiratory monitoring OR Portable monitor* OR screen* OR diagno* OR sensitivity OR specificity OR accuracy OR reliab* OR valid* OR reproducib* OR "false positive" OR "false negative") AND ("Sleep Apnea, Obstructive") [DISEASE] **(N=304)**

TREATMENT AND HARMS (180 of 296 imported to the screening/diag search results; 116 were duplicates with the Screening and Diag. Search – imported to Duplicates Library**)**
INFLECT EXACT "Interventional" [STUDY-TYPES] AND INFLECT EXACT ("Adult" OR "Senior") [AGE-GROUP] AND NOT "single group assignment" AND "Sleep Apnea, Obstructive" [DISEASE] AND (Positive-Pressure Respiration OR Continuous Positive Airway Pressure OR CPAP OR Intermittent Positive Pressure Ventilation OR IPPV OR Inspiratory Positive-Pressure Ventilation OR Inspiratory Positive Pressure Ventilation OR Biphasic Intermittent Positive Airway Pressure OR BiPAP OR Mandibular Prosthesis OR mandibular advancement device OR mandibular advancement devices OR Mandibular Advancement OR surgery OR surgical OR UPPP or uvulopalatopharyngoplasty OR septoplasty OR Pillar Procedure OR Hyoid advancement OR Osteotomy OR tonsillectomy OR exercise OR weight loss OR weight reduction OR diet) [TREATMENT] **(N=296)**

WHO ICTRP Advanced searches translated from the above, 6-18-15 through 6-24-15
Total from ICTRP in EndNote =422
Recruitment status: ALL
Condition box:
Obstructive sleep apnea
SCREENING AND DIAGNOSIS (N=85; all imported but I see a lot of CT.gov results)
Title box:
Ambulatory monitoring OR Polysomnograph* OR oximetr* OR diagnos* OR sleep monitoring OR PSG OR polygraphy OR Actigraphy OR Apnoescreen OR home monitor* OR Monitoring system* OR portable respiratory

monitoring OR Portable monitor* OR screen* OR diagno* OR sensitivity OR specificity OR accuracy OR reliab* OR valid* OR reproducib* OR "false positive" OR "false negative"

TREATMENT AND HARMS (N=229-289)
Must run 2 iterations to be able to search all of the terms that go into the Intervention box. When String 1 (321) and String 2 (68) were imported to previous results, 337 total were imported
Condition box:
Obstructive sleep apnea
Intervention box:
String 1:
Positive-Pressure Respiration OR Continuous Positive Airway Pressure OR CPAP OR Mandibular Prosthesis OR mandibular advancement device OR mandibular advancement devices OR Mandibular Advancement OR surgery
(N=321, 302 imported)
String 2:
surgical OR UPPP or uvulopalatopharyngoplasty OR septoplasty OR Pillar Procedure OR Hyoid advancement OR Osteotomy OR tonsillectomy OR exercise OR weight loss OR weight reduction OR diet
(N= 68, 35 imported)

Update Search Strategies

PubMed searches 10/26/15

PubMed Intervention/Treatment Search

Search	Query	Items Found
#1	Search "Sleep Apnea Syndromes"[MeSH] OR "Sleep Apnea, Obstructive"[MeSH] OR "Obstructive Sleep Apneas"[tw] OR "Obstructive Sleep Apnea"[tw] OR "Obstructive Sleep Apnea Syndrome"[tw] OR "Obstructive Sleep Apnoeas"[tw] OR "Obstructive Sleep Apnoea"[tw] OR OSAHS[tw] OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"[tw]	31091
#2	Search "Positive-Pressure Respiration"[Mesh:NoExp]	15320
#3	Search "Continuous Positive Airway Pressure"[Mesh]	4528
#4	Search ("Continuous Positive Airway Pressure"[tw] OR CPAP[tw])	10108
#5	Search "Intermittent Positive-Pressure Ventilation"[MeSH]	2041
#6	Search ("Intermittent Positive Pressure Ventilation"[tw] OR "IPPV"[tw] OR "Inspiratory Positive-Pressure Ventilation"[tw] OR "Inspiratory Positive Pressure Ventilation"[tw] OR "Biphasic Intermittent Positive Airway Pressure"[tw] OR BiPAP[tw])	3351
#7	Search "Mandibular Prosthesis"[MeSH Terms]	809
#8	Search ("mandibular advancement device"[tw] OR "mandibular advancement devices"[tw])	224
#9	Search "Mandibular Advancement/instrumentation"[Mesh]	563
#10	Search ("oral appliance"[tw] OR "oral appliances"[tw])	701
#11	Search ("General Surgery"[MeSH] OR "general surgery"[tw])	40999
#12	Search ("otolaryngology"[MeSH] OR "otolaryngology"[tw] OR "Otorhinolaryngology"[tw] OR "Laryngology"[tw])	18827
#13	Search ("surgery, plastic"[MeSH] OR "Plastic Surgery"[tw])	30637
#14	Search ("Surgical Procedures, Operative"[MeSH] OR "Operative Surgical Procedure"[tw] OR "Operative Surgical Procedures"[tw] OR "Operative Procedures"[tw] OR "Operative Procedure"[tw])	2507349
#15	Search "Bariatric Surgery"[Mesh]	16383
#16	Search (UPPP[tw] OR uvulopalatopharyngoplasty[tw])	969
#17	Search (septoplasty[tw] AND "turbinate reduction"[tw])	44
#18	Search ("Pillar Procedure"[tw] OR "soft palate implants"[tw])	0
#19	Search "Hyoid advancement"[tw]	11
#20	Search "Orthognathic Surgical Procedures"[Mesh]	1554
#21	Search "Osteotomy, Le Fort"[Mesh]	1646
#22	Search "Osteotomy, Sagittal Split Ramus"[Mesh]	405
#23	Search ("tonsillectomy"[MeSH] OR tonsillectomy[tw])	10083
#24	Search ("Exercise Therapy"[MeSH] OR exercise[MeSH] OR "exercise therapy"[tw] OR "exercise therapies"[tw])	153553
#25	Search ("weight loss"[MeSH] OR "weight loss"[tw] OR "weight reduction"[tw])	78219
#26	Search ("Body Mass Index"[Mesh] OR "body mass index"[tw] OR BMI[tw])	184751

Appendix B1. Detailed Methods

Search	Query	Items Found
#27	Search ("Obesity"[Mesh] OR obesity[tw])	222785
#28	Search "Diet, Reducing"[Mesh]	9720
#29	Search (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28)	3061634
#30	Search (#1 and #29)	16809
#31	Search ((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	616366
#32	Search (#30 and #31)	1163
#33	Search (#30 and #31) Filters: Humans	1111
#34	Search (#30 and #31) Filters: Humans; Adult: 19+ years	948
#35	Search (#30 and #31) Filters: Publication date from 2014/03/30 to 2015/10/26; Humans; Adult: 19+ years	74
#36	Search ("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields]))	1799790
#37	Search (#30 and #36)	4805
#38	Search (#30 and #36) Filters: Humans	4770
#39	Search (#30 and #36) Filters: Humans; Adult: 19+ years	3683
#40	Search (#30 and #36) Filters: Publication date from 2014/03/30 to 2015/10/26; Humans; Adult: 19+ years	375

PubMed Screening Search, 10-26-15

Search	Query	Items Found
#1	Search ("Sleep Apnea Syndromes"[MeSH] OR "Sleep Apnea, Obstructive"[MeSH] OR "Obstructive Sleep Apneas"[tw] OR "Obstructive Sleep Apnea"[tw] OR "Obstructive Sleep Apnea Syndrome"[tw] OR "Obstructive Sleep Apnoeas"[tw] OR "Obstructive Sleep Apnoea"[tw] OR OSAHS[tw] OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"[tw]))	31091
#2	Search "Questionnaires"[Mesh]	336040
#3	Search "Epworth Sleepiness Scale"[All Fields]	2465
#4	Search "STOP Questionnaire"[All Fields]	24
#5	Search "STOP-Bang Questionnaire"[All Fields]	65
#6	Search "Berlin Questionnaire"[All Fields]	295
#7	Search "Wisconsin Sleep Questionnaire"[All Fields]	5
#8	Search "Decision Support Techniques"[Mesh]	63509
#9	Search ("Clinical prediction tool" OR "Clinical prediction rule" OR "Clinical prediction score")	575
#10	Search "Multivariable Apnea Prediction Index"[All Fields]	9
#11	Search "Multivariable Apnoea Prediction Index"[All Fields]	0
#12	Search "Snoring Scale"[All Fields]	24
#13	Search "NAMES"[All Fields]	15214
#14	Search "Sleep Apnea Clinical Score"[All Fields]	12
#15	Search "Neck circumference"[All Fields]	726
#16	Search Mallampati[All Fields]	577
#17	Search "Craniofacial structure"[All Fields]	128
#18	Search "Nocturnal choking"[All Fields]	22
#19	Search "Nocturnal gasping"[All Fields]	3
#20	Search ("Body Mass Index"[Mesh]) OR "Body Weight"[Mesh] OR "Obesity"[Mesh])	410281
#21	Search ("Snoring"[Mesh] OR snoring)	5921
#22	Search Sleepiness	31499
#23	Search (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22)	837425
#24	Search (#1 and #23)	13656
#25	Search ("Mass Screening"[Mesh] OR screening[tiab])	410872
#26	Search "Predictive Value of Tests"[Mesh]	153814
#27	Search ("Diagnostic Tests, Routine"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "ROC Curve"[Mesh] OR "Diagnosis"[Mesh] OR "Reproducibility of	9240601

Appendix B1. Detailed Methods

Search	Query	Items Found
	Results"[Mesh] OR "False Negative Reactions"[Mesh] OR "False Positive Reactions"[Mesh] OR "predictive value"[tw] OR sensitivity[tw] OR specificity[tw] OR accuracy[tw] OR screen[tw] OR diagno*[tw] OR ROC[tw] OR reproducib*[tw] OR "false positive"[tw] OR "false negative"[tw] OR "likelihood ratio"[tw])	
#28	Search (#25 or #26 or #27)	9360197
#29	Search (#24 and #28)	11490
#30	Search (Autobiography[Publication Type] OR Bibliography[Publication Type] OR Biography[Publication Type] OR Case Reports[Publication Type] OR Classical Article[Publication Type] OR comment[Publication Type] OR Congresses[Publication Type] OR Consensus Development Conference[Publication Type] OR Dictionary[Publication Type] OR Directory[Publication Type] OR Editorial[Publication Type] OR Electronic supplementary materials[Publication Type] OR Festschrift[Publication Type] OR In Vitro[Publication Type] OR Interactive Tutorial[Publication Type] OR Interview[Publication Type] OR Lectures[Publication Type] OR Legal Cases[Publication Type] OR Legislation[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Newspaper article[Publication Type] OR Patient Education Handout[Publication Type] OR Personal Narratives[Publication Type] OR Periodical Index[Publication Type] OR Pictorial works[Publication Type] OR Popular works[Publication Type] OR Portraits[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type] OR Webcasts[Publication Type])	3475802
#31	Search (#29 NOT #30)	10194
#32	Search (#29 NOT #30) Filters: Adult: 19+ years	6552
#33	Search (#29 NOT #30) Filters: Humans; Adult: 19+ years	6552
#34	Search (#29 NOT #30) Filters: Publication date from 2014/03/29 to 2015/10/26; Humans; Adult: 19+ years	407
#35	Search (#29 NOT #30) Filters: Publication date from 2014/03/29 to 2015/10/26; Humans; English; Adult: 19+ years	389
#36	Search (#34 NOT #35) Non-English	18

PubMed KQ6 (AHI) search update, 10-26-15

Search	Query	Items Found
#1	Search ("Sleep Apnea Syndromes"[MeSH] OR "Sleep Apnea, Obstructive"[MeSH] OR "Obstructive Sleep Apneas"[tw] OR "Obstructive Sleep Apnea"[tw] OR "Obstructive Sleep Apnea Syndrome"[tw] OR "Obstructive Sleep Apnoeas"[tw] OR "Obstructive Sleep Apnoea"[tw] OR OSAHS[tw] OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"[tw]))	31091
#2	Search ("Apnea hypopnea Index"[All Fields] OR "Apnea/hypopnea index"[All Fields] OR "Apnoea hypopnea index"[All Fields] OR "Apnoea hypopnoea index"[All Fields] OR "Apnoea/hypopnoea index"[All Fields])	5420
#3	Search (#1 and #2)	5228
#4	Search ("Patient Outcome Assessment"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Fatal Outcome"[Mesh])	815297
#5	Search outcome*[tiab]	1078898
#6	Search ("Mortality"[Mesh] OR "mortality" [Subheading] OR mortality[tiab]))	929218
#7	Search ("Quality of Life"[Mesh] OR "quality of life"[tiab])	216756
#8	Search ("Motor Vehicles"[Mesh] OR "motor vehicle"[tiab] OR "motor vehicles"[tiab])	26220
#9	Search ("Cardiovascular Diseases"[Mesh]) OR "Myocardial Infarction"[Mesh] OR cardiovascular*[tiab])	2105237
#10	Search ("Stroke"[Mesh]) OR "Cerebrovascular Disorders"[Mesh] OR stroke[tiab] OR cerebrovasc*[tiab]))	385822
#11	Search "heart failure"[tiab]	123422
#12	Search ("Headache"[Mesh] OR headache[tiab]))	65056
#13	Search ("Mild Cognitive Impairment"[Mesh]) OR "Cognition Disorders"[Mesh] OR cognit*[tiab])	278023
#14	Search (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)	4353340
#15	Search (#3 and #14)	2740
#16	Search (Autobiography[Publication Type] OR Bibliography[Publication Type] OR Biography[Publication Type] OR Case Reports[Publication Type] OR Classical Article[Publication Type] OR comment[Publication Type] OR Congresses[Publication Type] OR Consensus Development Conference[Publication Type] OR Dictionary[Publication Type] OR Directory[Publication Type] OR Editorial[Publication Type] OR Electronic supplementary	3475802

Appendix B1. Detailed Methods

Search	Query	Items Found
	materials[Publication Type] OR Festschrift[Publication Type] OR In Vitro[Publication Type] OR Interactive Tutorial[Publication Type] OR Interview[Publication Type] OR Lectures[Publication Type] OR Legal Cases[Publication Type] OR Legislation[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Newspaper article[Publication Type] OR Patient Education Handout[Publication Type] OR Personal Narratives[Publication Type] OR Periodical Index[Publication Type] OR Pictorial works[Publication Type] OR Popular works[Publication Type] OR Portraits[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type] OR Webcasts[Publication Type] OR Twin Studies[Publication Type])	
#17	Search (#15 NOT #16)	2690
#18	Search (#15 NOT #16) Filters: Adult: 19+ years	2052
#19	Search (#15 NOT #16) Filters: Humans; Adult: 19+ years	2052
#20	Search (#15 NOT #16) Filters: Publication date from 2014/03/30 to 2015/10/26; Humans; Adult: 19+ years	201

PubMed Diagnosis search update, 10-26-15

Search	Query	Items Found
#1	Search ("Sleep Apnea Syndromes"[MeSH] OR "Sleep Apnea, Obstructive"[MeSH] OR "Obstructive Sleep Apneas"[tw] OR "Obstructive Sleep Apnea"[tw] OR "Obstructive Sleep Apnea Syndrome"[tw] OR "Obstructive Sleep Apnoeas"[tw] OR "Obstructive Sleep Apnoea"[tw] OR OSAHS[tw] OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"[tw]))	31091
#2	Search "Sleep Apnea Syndromes/diagnosis"[Majr]	4804
#3	Search "Sleep Apnea, Obstructive/diagnosis"[Majr]	2550
#4	Search "Monitoring, Ambulatory/instrumentation"[Majr]	3293
#5	Search (Polysomnography[Mesh] OR Polysomnographies[tw])	15308
#6	Search (oximetry[MeSH] OR oximetry[tw] OR "Oximetries"[tw])	15759
#7	Search "Diagnostic Tests, Routine"[Mesh]	7624
#8	Search "sleep monitoring"[All Fields]	286
#9	Search PSG	3975
#10	Search polygraphy	547
#11	Search Actigraphy	3170
#12	Search Apnoescreen	4
#13	Search (home AND monitor*)	14258
#14	Search Monitoring system*	9502
#15	Search "portable respiratory monitoring"	4
#16	Search Portable monitor*	344
#17	Search ("diagnosis"[MeSH] OR "diagnosis"[tw] OR "diagnoses"[tw] OR "Reproducibility of Results"[MeSH] OR "Reproducibility of Results"[tw] OR "Reproducibility of Findings"[tw] OR "Predictive Value of Tests"[Mesh] OR "Predictive Value"[tw] OR "ROC Curve"[Mesh] OR "ROC"[tw] OR "Validity of Results"[tw] OR reliab*[tw] OR valid*[tw] OR "False Negative Reactions"[MeSH] OR "false negative"[tw] OR "False Positive Reactions"[MeSH] OR "false positive"[tw] OR "accuracy"[tw] OR reproducib*[tw] OR "likelihood ratio"[tw] OR "accuracy"[tw] OR "sensitivity"[tw] OR "specificity"[tw])	9196706
#18	Search (#1 AND (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17))	22367
#19	Search (#1 AND (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17)) Filters: Humans	20874
#20	Search (#1 AND (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17)) Filters: Publication date from 2014/03/29 to 2015/10/26; Humans	1383
#21	Search (Autobiography[Publication Type] OR Bibliography[Publication Type] OR Biography[Publication Type] OR Case Reports[Publication Type] OR Classical Article[Publication Type] OR comment[Publication Type] OR Congresses[Publication Type] OR Consensus Development Conference[Publication Type] OR Dictionary[Publication Type] OR Directory[Publication Type] OR Editorial[Publication Type] OR Electronic supplementary materials[Publication Type] OR Festschrift[Publication Type] OR In Vitro[Publication Type] OR Interactive Tutorial[Publication Type] OR Interview[Publication Type] OR Lectures[Publication Type] OR Legal Cases[Publication Type] OR Legislation[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Newspaper article[Publication Type] OR Patient Education Handout[Publication Type] OR Personal Narratives[Publication Type] OR Periodical	3475802

Appendix B1. Detailed Methods

Search	Query	Items Found
	Index[Publication Type] OR Pictorial works[Publication Type] OR Popular works[Publication Type] OR Portraits[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type] OR Webcasts[Publication Type])	
#22	Search (#20 NOT #21)	1192
#23	Search (#20 NOT #21) Filters: Adult: 19+ years	769

Cochrane Library Interventions/Tx search update, 10-26-15

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] or [mh "Sleep Apnea, Obstructive"] or [mh "Obstructive Sleep Apneas"] or [mh "Obstructive Sleep Apnea"] or [mh "Obstructive Sleep Apnea Syndrome"] or "Obstructive Sleep Apnoeas" or "Obstructive Sleep Apnoea" or OSAHS or ("sleep apnea" and hypopnea) or "sleep disordered breathing"	2386
#2	[mh ^"Positive-Pressure Respiration"]	1266
#3	[mh "Continuous Positive Airway Pressure"]	696
#4	"Continuous Positive Airway Pressure" or CPAP	2810
#5	[mh "Intermittent Positive-Pressure Ventilation"]	195
#6	"Intermittent Positive Pressure Ventilation" or "IPPV" or "Inspiratory Positive-Pressure Ventilation" or "Inspiratory Positive Pressure Ventilation" or "Biphasic Intermittent Positive Airway Pressure" or BiPAP	662
#7	[mh "Mandibular Prosthesis"]	6
#8	"mandibular advancement device" or "mandibular advancement devices"	56
#9	[mh "Mandibular Advancement"]	130
#10	[mh "General Surgery"] or "general surgery"	2312
#11	[mh otolaryngology] or otolaryngology or Otorhinolaryngology or Laryngology	6541
#12	[mh "Surgery, Plastic"] or "Plastic Surgery"	1400
#13	[mh "Surgical Procedures, Operative"] or "Operative Surgical Procedure" or "Operative Surgical Procedures" or "Operative Procedures" or "Operative Procedure"	102778
#14	[mh "Bariatric Surgery"]	823
#15	UPPP or uvulopalatopharyngoplasty	115
#16	(septoplasty and "turbinate reduction")	3
#17	"Pillar Procedure" or "soft palate implants"	1
#18	"Hyoid advancement"	0
#19	[mh "Orthognathic Surgical Procedures"]	67
#20	[mh "Osteotomy, Le Fort"]	67
#21	[mh "Osteotomy, Sagittal Split Ramus"]	18
#22	[mh tonsillectomy] or tonsillectomy	1890
#23	[mh "Exercise Therapy"] or [mh exercise] or "exercise therapy" or "exercise therapies"	20172
#24	[mh "weight loss"] or "weight loss" or "weight reduction"	11104
#25	[mh "Body Mass Index"] or "body mass index" or BMI	22489
#26	[mh Obesity] or obesity	16993
#27	[mh "Diet, Reducing"]	1627
#28	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27	161973
#29	#1 and #28	1642
#30	#29 Publication Year from 2014 to 2015, in in Cochrane Reviews, Other Reviews, Trials and Technology Assessments	253

Cochrane Library Screening update, 10-26-15

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] or [mh "Sleep Apnea, Obstructive"] or [mh "Obstructive Sleep Apneas"] or [mh "Obstructive Sleep Apnea"] or [mh "Obstructive Sleep Apnea Syndrome"] or "Obstructive Sleep Apnoeas" or "Obstructive Sleep Apnoea" or OSAHS or ("sleep apnea" and hypopnea) or "sleep disordered breathing"	2386
#2	[mh Questionnaires]	17769
#3	"Epworth Sleepiness Scale"	573
#4	"STOP Questionnaire"	2
#5	"STOP-Bang Questionnaire"	2
#6	"Berlin Questionnaire"	18
#7	"Wisconsin Sleep Questionnaire"	1

Appendix B1. Detailed Methods

ID	Search	Hits
#8	[mh "Decision Support Techniques"]	3255
#9	"Clinical prediction tool" or "Clinical prediction rule" or "Clinical prediction score"	81
#10	"Multivariable Apnea Prediction Index"	0
#11	"Multivariable Apnoea Prediction Index"	0
#12	"Snoring Scale"	4
#13	"NAMES"	1844
#14	"Sleep Apnea Clinical Score"	2
#15	"Neck circumference"	68
#16	Mallampati	128
#17	"Craniofacial structure"	3
#18	"Nocturnal choking"	1
#19	"Nocturnal gasping"	1
#20	[mh "Body Mass Index"] or [mh "Body Weight"] or [mh Obesity]	19723
#21	[mh Snoring] or snoring	458
#22	Sleepiness	2207
#23	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #21 or #22	25182
#24	#1 and #23	801
#25	[mh "Mass Screening"] or screening	24181
#26	[mh "Predictive Value of Tests"]	6376
#27	[mh "Diagnostic Tests, Routine"] or [mh "Sensitivity and Specificity"] or [mh "Predictive Value of Tests"] or [mh "ROC Curve"] or [mh Diagnosis] or [mh "Reproducibility of Results"] or [mh "False Negative Reactions"] or [mh "False Positive Reactions"] or "predictive value" or sensitivity or specificity or accuracy or screen* or diagno* or ROC or reproducib* or "false positive" or "false negative" or "likelihood ratio"	355349
#28	#25 or #26 or #27	355433
#29	#24 and #28 Publication Year from 2014 to 2015, in Cochrane Reviews, Other Reviews, Trials and Technology Assessments	75

Cochrane Library KQ6 (AHI) search update, 10-26-15

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] or [mh "Sleep Apnea, Obstructive"] or [mh "Obstructive Sleep Apneas"] or [mh "Obstructive Sleep Apnea"] or [mh "Obstructive Sleep Apnea Syndrome"] or "Obstructive Sleep Apnoeas" or "Obstructive Sleep Apnoea" or OSAHS or ("sleep apnea" and hypopnea) or "sleep disordered breathing"	2386
#2	"Apnea hypopnea Index" or "Apnea/hypopnea index" or "Apnoea hypopnea index" or "Apnoea hypopnoea index" or "Apnoea/hypopnoea index"	797
#3	#1 and #2	742
#4	[mh "Patient Outcome Assessment"] or [mh "Outcome Assessment (Health Care)"] or [mh "Fatal Outcome"]	102609
#5	outcome*	240219
#6	[mh Mortality] or mortality	56244
#7	[mh "Quality of Life"] or "quality of life"	44998
#8	[mh "Motor Vehicles"] or "motor vehicle" or "motor vehicles"	679
#9	[mh "Cardiovascular Diseases"] or [mh "Myocardial Infarction"] or cardiovascular*	106030
#10	[mh Stroke] or [mh "Cerebrovascular Disorders"] or stroke or cerebrovasc*	45504
#11	"heart failure"	15167
#12	[mh Headache] or headache	18758
#13	[mh "Mild Cognitive Impairment"] or [mh "Cognition Disorders"] or cognit*	36402
#14	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	388817
#15	#3 and #14 Publication Year from 2014 to 2015, in Cochrane Reviews, Other Reviews, Trials and Technology Assessments	67

Appendix B1. Detailed Methods

Cochrane Library Diagnosis search update, 10-26-15

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] or [mh "Sleep Apnea, Obstructive"] or [mh "Obstructive Sleep Apneas"] or [mh "Obstructive Sleep Apnea"] or [mh "Obstructive Sleep Apnea Syndrome"] or "Obstructive Sleep Apnoeas" or "Obstructive Sleep Apnoea" or OSAHS or ("sleep apnea" and hypopnea) or "sleep disordered breathing"	2386
#2	[mh ^"Monitoring, Ambulatory"/IS]	128
#3	[mh Polysomnography] or Polysomnographies	1371
#4	[mh oximetry] or oximetry or Oximetries	1927
#5	[mh "Diagnostic Tests, Routine"]	331
#6	"sleep monitoring"	42
#7	PSG	566
#8	polygraphy	50
#9	Actigraphy	572
#10	Apnoescreen	1
#11	home and monitor*	3574
#12	Monitoring system*	9320
#13	"portable respiratory monitoring"	3
#14	Portable monitor*	443
#15	[mh diagnosis] or diagnosis or diagnoses or [mh "Reproducibility of Results"] or "Reproducibility of Results" or "Reproducibility of Findings" or [mh "Predictive Value of Tests"] or "Predictive Value" or [mh "ROC Curve"] or ROC or "Validity of Results" or reliab* or valid* or [mh "False Negative Reactions"] or "false negative" or [mh "False Positive Reactions"] or "false positive" or accuracy or reproducib* or "likelihood ratio" or "accuracy" or "sensitivity" or "specificity"	350315
#16	#1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)	1529
#17	#16 Publication Year from 2014 to 2015, in Cochrane Reviews, Other Reviews, Trials and Technology Assessments	165

EMBASE searches 10-26-15 (Intervention & Harms) and 10-27-15 (Screening)

Intervention search
Benefits – 217, 169 imported
Harms – 151, 75 imported

No.	Query	Results
#32	#28 AND #31	151
#31	'cohort analysis'/exp OR 'epidemiological study' OR (cohort AND (study OR studies)) OR 'prospective study'/exp OR (prospective* AND cohort)	736,749
#30	#28 AND #29	217
#29	'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'random allocation'/exp OR 'controlled trial'/exp OR 'control trial' OR ('control':ab,ti OR 'controlled':ab,ti AND 'trial':ab,ti)	5,048,338
#28	#27 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	656
#27	#26 AND [humans]/lim AND [6-4-2014]/sd NOT [26-10-2015]/sd	2,405
#26	#4 AND #25	11,198
#25	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	200,411
#24	'weight reduction'/exp	117,483
#23	'tonsillectomy'/exp	12,449
#22	'sagittal split ramal osteotomy'/exp	236
#21	'maxilla osteotomy'/exp	2,282
#20	'orthognathic surgery'/exp	2,019
#19	'hyoid advancement'	20
#18	'pillar procedure' OR 'soft palate implants'	8
#17	'nose septum reconstruction'/exp AND 'turbinate reduction'	41
#16	'uvulopalatopharyngoplasty'/exp	1,276
#15	'bariatric surgery'/exp	23,670
#14	'otorhinolaryngology'/exp	22,128
#13	'general surgery'/exp	10,791
#12	'mandible reconstruction'/exp	4,303
#11	'mandibular advancement device' OR 'mandibular advancement devices'	315
#10	'mandible prosthesis'/exp	676

#9	'intermittent positive pressure ventilation' OR 'ippv' OR 'inspiratory positive-pressure ventilation' OR 'inspiratory positive pressure ventilation' OR 'biphasic intermittent positive airway pressure' OR bipap	5,180
#8	'intermittent positive pressure ventilation'/exp	2,895
#7	'positive end expiratory pressure'/exp/mj	12,783
#6	'cpap device'/exp	289
#5	'positive end expiratory pressure'/exp/mj	12,783
#4	#1 OR #2 OR #3	50,880
#3	'sleep apnea' AND hypopnea	9,473
#2	'obstructive sleep apnoeas' OR 'obstructive sleep apnoea'	5,288
#1	'sleep disordered breathing'/exp	50,425

EMBASE Screening search, 10-27-15

37 results, 28 imported

No.	Query	Results
#21	#16 NOT #17 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim AND [english]/lim AND [7-10-2014]/sd NOT [27-10-2015]/sd	37
#20	#16 NOT #17 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim AND [english]/lim	355
#19	#16 NOT #17 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim	389
#18	#16 NOT #17	675
#17	#8 AND #15 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim)	930
#16	#8 AND #15	1,605
#15	#9 OR #10 OR #11 OR #12 OR #13 OR #14	5,416,056
#14	'diagnosis'/exp	5,218,583
#13	'receiver operating characteristic'/exp	59,873
#12	'sensitivity and specificity'/exp	228,199
#11	'diagnostic test'/exp	760,098
#10	'predictive value'/exp	78,645
#9	'mass screening'/exp	174,071
#8	#4 AND #7	4,672
#7	#5 OR #6	463,378
#6	'clinical prediction tool' OR 'clinical prediction rule' OR 'clinical prediction score'	866
#5	'questionnaire'/exp	462,559
#4	#1 OR #2 OR #3	51,523
#3	'sleep apnea' AND hypopnea	9,473
#2	'obstructive sleep apnoeas' OR 'obstructive sleep apnoea'	5,288
#1	'sleep disordered breathing'/exp OR 'sleep disordered breathing'	51,108

CT.gov and ICTRP searches for OSA Oct 2015

All searches done Oct. 28, 2015
Total number in EndNote = 120
Duplicates library = 22

ClinicalTrials.gov Expert searches

Screening/Diagnosis combined search:
67 results, all imported
INFLECT EXACT ("Adult" OR "Senior") [AGE-GROUP] AND (Ambulatory monitoring OR Polysomnograph* OR oximetr* OR diagnos* OR sleep monitoring OR PSG OR polygraphy OR Actigraphy OR Apnoescreen OR home monitor* OR Monitoring system* OR portable respiratory monitoring OR Portable monitor* OR screen* OR diagno* OR sensitivity OR specificity OR accuracy OR reliab* OR valid* OR reproducib* OR "false positive" OR "false negative") AND "Sleep Apnea, Obstructive" | updated from 06/18/2015 to 10/28/2015

Appendix B1. Detailed Methods

Treatment and Harms combined search:
62 results, 40 imported and 22 went to Duplicates Library
INFLECT EXACT "Interventional" [STUDY-TYPES] AND INFLECT EXACT ("Adult" OR "Senior") [AGE-GROUP] AND NOT "single group assignment" | "Sleep Apnea, Obstructive" | Positive-Pressure Respiration OR Continuous Positive Airway Pressure OR CPAP OR Intermittent Positive Pressure Ventilation OR IPPV OR Inspiratory Positive-Pressure Ventilation OR Inspiratory Positive Pressure Ventilation OR Biphasic Intermittent Positive Airway Pressure OR BiPAP OR Mandibular Prosthesis OR mandibular advancement device OR mandibular advancement devices OR Mandibular Advancement OR surgery OR surgical OR UPPP or uvulopalatopharyngoplasty OR septoplasty OR Pillar Procedure OR Hyoid advancement OR Osteotomy OR tonsillectomy OR exercise OR weight loss OR weight reduction OR diet | updated from 06/18/2015 to 10/28/2015

WHO ICTRP Advanced Searches
Limited to ALL trials and dates 6-18-15 – 10-28-15

SCREENING AND DIAGNOSIS (N=0)
Condition box:
Obstructive sleep apnea
Title box:
Ambulatory monitoring OR Polysomnograph* OR oximetr* OR diagnos* OR sleep monitoring OR PSG OR polygraphy OR Actigraphy OR Apnoescreen OR home monitor* OR Monitoring system* OR portable respiratory monitoring OR Portable monitor* OR screen* OR diagno* OR sensitivity OR specificity OR accuracy OR reliab* OR valid* OR reproducib* OR "false positive" OR "false negative"

Treatment and Harms search: (13 total, all imported)
Terms do not all fit in the intervention box so they were broken into two searches
Condition box:
Obstructive sleep apnea
Intervention box:
String 1:
Positive-Pressure Respiration OR Continuous Positive Airway Pressure OR CPAP OR Mandibular Prosthesis OR mandibular advancement device OR mandibular advancement devices OR Mandibular Advancement OR surgery
(N=11, all imported)
String 2:
surgical OR UPPP or uvulopalatopharyngoplasty OR septoplasty OR Pillar Procedure OR Hyoid advancement OR Osteotomy OR tonsillectomy OR exercise OR weight loss OR weight reduction OR diet
(N= 2, all imported)

Appendix B2. Eligibility Criteria

	Include	Exclude
Populations	Adults ages 18 years or older **KQs 1, 2:** Asymptomatic adults and persons with unrecognized symptoms of OSA **KQs 3, 7:** Asymptomatic adults, persons with unrecognized symptoms of OSA, and referral populations **KQs 4–6, 8:** Persons with a confirmed diagnosis of OSA; population may include asymptomatic and/or symptomatic adults OSA severity will be defined as mild if the AHI (or RDI) is ≥5 to <15, moderate if the AHI (or RDI) is ≥15 to ≤30, and severe if the AHI (or RDI) is ≥30	Children and adolescents, pregnant women, studies of adults with acute stroke or other acute conditions that can trigger onset of OSA Studies focused on screening, diagnosis, or treatment of OSA among persons with a rare condition (e.g., acromegaly) **KQs 4–6, 8:** Studies of persons with suspected but unconfirmed OSA
Setting	Studies conducted in countries categorized as "Very High" on the Human Development Index, as defined by the United Nations Development Programme **KQs 4, 5, 8:** For nonsurgical interventions, studies must evaluate use at home rather than in a laboratory or facility (although the testing and outcome assessments may occur in sleep laboratories or other settings)	**KQs 4, 5, 8:** For nonsurgical treatments, interventions studied only in laboratories (e.g., studies of CPAP conducted in sleep laboratories)
Screening	Screening with the Epworth Sleepiness Scale, STOP Questionnaire, Berlin Questionnaire, Wisconsin Sleep Questionnaire, or STOP-BANG Questionnaire Risk stratification or clinical prediction tools that include multiple factors (e.g., the Multivariable Apnea Prediction Index); may include findings from physical examination (e.g., neck circumference, Mallampati classification) **KQ 2b:** Combined screening approaches, which may use a questionnaire or clinical prediction tool followed by home-based testing for persons who score above a defined threshold on the questionnaire or clinical prediction tool	Studies assessing single patient characteristics or risk factors
Diagnostic testing	Polysomnography conducted in a sleep laboratory, reviewed and interpreted by a qualified physician (the reference standard) Portable monitors used for home-based testing (including Type II, III, and IV monitors) Home-based testing followed by polysomnography	
Treatment/ management interventions	CPAP, mandibular advancement devices, surgery, and weight loss programs Variations of fixed oral CPAP are eligible, including auto-titrating CPAP, nasal CPAP, bilevel CPAP, and humidification with CPAP	Atrial overdrive pacing, medications, palatal implants, oropharyngeal exercises, tongue-retaining devices, positional alarms, nasal dilator strips, acupuncture, auricular plaster, and all other interventions not listed as included Medications to treat sleepiness, sleep quality, or bruxism (rather than used to treat OSA), such as armodafinil, bromocriptine, donepezil, eszopiclone, and modafinil Nasal steroids for treatment of allergic rhinitis or similar treatments that might secondarily improve OSA by treating another condition Studies focusing on potential worsening of OSA caused by treatment for another condition (e.g., use of testosterone for hypogonadism, use of medications that may cause weight gain)

Appendix B2. Eligibility Criteria

	Include	Exclude
Comparisons	**KQ 1:** Screened vs. nonscreened groups **KQ 2:** Overnight polysomnography conducted in a sleep laboratory; studies may also determine or compare persons at increased, average, or decreased risk or persons at higher and lower risk for OSA **KQ 3:** Studies on accuracy of screening must include a comparison with polysomnography; studies on reliability of screening must include measures of reproducibility (e.g., test-retest, comparison between different laboratories or readers) **KQs 4, 5, 8:** CPAP vs. control or sham CPAP; mandibular advancement devices vs. no treatment or inactive mandibular advancement devices; surgery vs. sham, conservative treatment, or no treatment; and weight loss interventions vs. control **KQ 6:** Persons with a higher or lower AHI **KQ 7:** Screened vs. nonscreened groups or groups undergoing screening and/or diagnostic testing vs. groups not undergoing screening and/or diagnostic testing	No comparison; nonconcordant historical controls; comparative studies of various interventions (e.g., comparing CPAP with mandibular advancement devices or comparing different types of CPAP) **KQs 2, 3:** Studies with verification bias in which only a subgroup had polysomnography as the comparator
Outcomes	**KQs 1, 5, 6:** Mortality, quality of life (both disease-specific measures, such as the Functional Outcomes of Sleep Questionnaire, and general measures, such as the 36-Item Short-Form Health Survey), motor vehicle crashes, cardiovascular events (including ischemic events and rhythm disturbances, such as atrial fibrillation), cerebrovascular events, incidence of heart failure, headaches, cognitive impairment **KQ 2:** Sensitivity, specificity, discrimination, calibration **KQ 3:** Sensitivity and specificity; measures of reproducibility (e.g., test-retest, comparison between different laboratories or readers) **KQ 4:** Change in AHI, blood pressure, and daytime somnolence or sleepiness (e.g., as measured by the Epworth Sleepiness Scale or other validated measures) **KQ 7:** False-positive results leading to unnecessary treatment, anxiety, condition-specific distress, or stigma **KQ 8:** Rash, irritation, need for additional sleep medications (e.g., to tolerate CPAP), claustrophobia, oral or nasal dryness, epistaxis, pain, excess salivation, tooth damage or loosening, complications of surgery (e.g., perioperative death, hemorrhage, nerve palsy, additional emergency surgery, cardiovascular events, respiratory failure, rehospitalization, speech or voice changes, difficulty swallowing, airway stenosis)	
Study designs	**KQ 1:** RCTs comparing screened vs. nonscreened groups **KQ 2:** Prospective cohort studies and cross-sectional studies that develop or evaluate screening questionnaires or clinical prediction tools Previously published systematic reviews (only for the purposes of identifying existing studies) Clinical prediction tools and screening questionnaires must be externally validated **KQ 3:** Good-quality, recent (within 5 years) systematic reviews comparing diagnostic tests with formal, attended polysomnography conducted in a sleep laboratory Primary studies published after the search cutoff of the most recent systematic review will be included (i.e., bridge searches will be performed to determine whether there is new evidence since the review and whether it is consistent with the review) **KQs 4, 5:** RCTs; previously published systematic reviews	All other designs **KQs 2, 3:** Questionnaires, tools, and tests not validated in a group of participants separate from the sample used to develop the test

Appendix B2. Eligibility Criteria

	Include	Exclude
	(only for the purposes of identifying existing studies) **KQ 6:** Good-quality, recent (within 5 years) systematic reviews; bridge searches will be performed to determine whether there is new evidence since the review and whether it is consistent with the review Prospective cohort studies that follow participants for at least 1 year and are published after the search cutoff of the most recent systematic review will be included Treatment studies included in KQ 4 or 5 that report both change in AHI and change in a health outcome **KQ 7:** Studies eligible for KQ 1, 2, or 3 that report harms of screening or diagnostic tests **KQ 8:** RCTs for all interventions; prospective cohort studies with at least 100 participants that report harms of surgical interventions	
Language	English	Languages other than English

AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; KQ = Key Question; OSA = obstructive sleep apnea; RCT = randomized, controlled trial; RDI = respiratory disturbance index.

Randomized Controlled Trials

Criteria

- Initial assembly of comparable groups: Randomized controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: Equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Sources: U.S. Preventive Services Task Force, Procedure Manual, Appendix VII http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual---appendix-vii
Harris et al., 2001[285]

Studies of Screening Tests

Criteria

- Screening test relevant, available for primary care, adequately described.
- Study uses a credible reference standard, performed regardless of test results.
- Reference standard interpreted independently of screening test.
- Handles indeterminate results in a reasonable manner.
- Spectrum of patients included in study.
- Sample size: Although this is one of the criteria listed in the current procedures manual, we did not consider sample size when assessing study quality, as sample size affects precision of the estimate.
- Administration of reliable screening test.

In addition to the criteria listed in the USPSTF procedures manual, we also considered the criteria described in our Appendix D (which details quality assessments of individual studies).

Definition of Ratings Based on Above Criteria

Good: Relevant and adequately described study populations for the outcome of interest (i.e., Sensitivity, Specificity), screening test well described in terms of test procedures followed and threshold used for a "positive" or "negative" test, credible reference standard used for outcome of interest (i.e., Sensitivity or Specificity), generally interprets reference standard independently of screening test, outcomes clearly reported and valid, handles indeterminate results in a reasonable manner.

Fair: Mostly includes a relevant and adequately described study population for the outcome of interest (i.e., Sensitivity, Specificity), screening test described although may include some ambiguity about test procedures followed or threshold for a "positive" or "negative" test, credible reference standard mostly used for outcome of interest (i.e., Sensitivity or specificity), interpretation of reference standard may or may not be independent of screening test, outcomes mostly clearly reported although may have some ambiguity regarding how indeterminate results were handled.

Poor: Has fatal flaw such as study population not appropriate for outcome of interest (i.e., Sensitivity, Specificity), screening test improperly administered or not at all described, use of noncredible reference standard, reference and screening test not independently assessed, outcomes not clearly or accurately reported with no information about how indeterminate tests were handled.

Criteria Adapted from: U.S. Preventive Services Task Force, Procedure Manual Appendix VII http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual---appendix-vii
Harris et al., 2001.[285]

Appendix B4. Outcome Measures and Instruments

Abbreviated Name	Complete Name	Description	Range/Meaning of Possible Scores	Improvement Indicated by
BQ	Berlin Questionnaire	Questionnaire consists of 3 categories (10 questions total) related to the risk of having sleep apnea.	Patients can be classified into High Risk or Low Risk	NA (screening instrument)
ESS	Epworth Sleepiness Scale	8-question measure of general level of daytime sleepiness or average sleep propensity in daily life	0 to 24	Decrease
EQ-5D	European Quality of Life Index	Assesses 5 dimensions of health status: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; yields a single index value for health status	-0.1 to 1.0	Increase
FOSQ and FOSQ-10	Functional Outcomes of Sleep Questionnaire	Assesses the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these abilities are improved by effective treatment (30- and 10-item versions)	5 to 20 (both versions)[a]	Increase
MCS	Mental Health Component Score of the SF-36	Summary measure that aggregates 4 mental/emotional health domains	0 to 100 (mean)	Increase
MVAP Score	Multivariable Apnea Prediction Score	Screening tool for sleep apnea based on the reporting of the frequency of various symptoms plus age, body mass index and gender	0 to 1; risk increases as score increases	NA (screening instrument)
NHP	Nottingham health profile	38-item instrument that measures subjective health status across the following domains: sleep, mobility, energy, pain, emotional reactions, social isolation	0 to 100	Decrease
PCS	Physical Health Component Score of the SF-36	Summary measure that aggregates 4 physical health domains	0 to 100 (mean)	Increase
SAQLI	Calgary Sleep Apnea Quality of Life Index	35-item tool to assess OSA-related quality of life across 4 domains: daily functioning, social interactions, emotional functioning, symptoms. An optional 5th domain assesses treatment-related symptoms	1 to 7	Increase
SF-36	Medical Outcome Short Form (36) Health Survey (SF-36)	36-item scale of patient health status. Administration time less than 15 minutes	0 to 100 (mean)	Increase

[a] Most published studies determine the total score by calculating the mean of the 5 subscale scores (each subscale score ranges from 1 to 4) and multiplying by 5, giving a total score range of 5 to 20. However, some published studies report the mean of the subscale scores without multiplying by 5 (resulting in a total score range of 1 to 4) and others report the sum of all the individual responses (resulting in a total score range of 0 to 120).

Berlin Questionnaire

1. Complete the following:

Height: _____ Weight: _____

Age: _____ Gender: ____M ____F

2. Do you snore?
_____Yes
_____No
_____Don't know

If you snore:

3. Your snoring is…
_____ Slightly louder than breathing
_____ As loud as talking
_____ Louder than talking
_____ Very loud, can be heard in adjacent rooms

4. How often do you snore?
_____ Nearly every day
_____ 3-4 times a week
_____ 1-2 times a week
_____ 1-2 times a month
_____ never or nearly never

5. Has your snoring ever bothered other people?
_____ Yes
_____ No

6. Has anyone noticed that you quit breathing during your sleep?
_____ Nearly every day.
_____ 3-4 times a week
_____ 1-2 times a week
_____ 1-2 times a month
_____ never or nearly never

7. How often do you feel tired or fatigued after your sleep?
_____ Nearly every day
_____ 3-4 times a week
_____ 1-2 times a week
_____ 1-2 times a month
_____ never or nearly never

8. During your wake time, do you feel tired, fatigued, or not up to par?
_____ Nearly every day
_____ 3-4 times a week
_____ 1-2 times a week
_____ 1-2 times a month
_____ never or nearly never

9. Have you ever nodded off or fallen asleep while driving a vehicle?
_____ Yes
_____ No
_____ If yes, how often does it occur?
_____ Nearly every day.
_____ 3-4 times a week
_____ 1-2 times a week
_____ 1-2 times a month
_____ never or nearly never

10. Do you have high blood pressure?
_____ Yes
_____ No
_____ Don't know

BMI (Body mass index) = _____

(see next page for scoring instructions)

Scoring the Berlin Questionnaire
The questionnaire consists of 3 categories related to the risk of having sleep apnea. Patients can be classified into High Risk or Low Risk based on their responses to the individual items and their overall scores in the symptom categories.

Categories and Scoring:

Category 1: items 2, 3, 4, 5, and 6;
Item 2: if '**Yes'**, assign **1 point**
Item 3: if either of the last two options is the response, assign **1 point**
Item 4: if either of the first two options is the response, assign **1 point**
Item 5: if **'Yes'** is the response, assign **1 point**
Item 6: if either of the first two options is the response, assign **2 points**
Add points. Category 1 is positive if the total score is 2 or more points.

Category 2: items 7, 8, and 9.
Item 7: if either of the first two options is the response, assign **1 point**
Item 8: if either of the first two options is the response, assign **1 point**
Item 9: if **'Yes'** is the response, assign **1 point**
Add points. Category 2 is positive if the total score is 2 or more points.

Category 3 is positive if the answer to item 10 is 'Yes' or if the BMI of the patient is greater than 30kg/m2. (BMI is defined as weight (kg) divided by height (m) squared, i.e.., kg/m2).

High Risk: if there are 2 or more categories where the score is positive.
Low Risk: if there is only 1 or no categories where the score is positive.

Additional Question: item 9 should be noted separately.

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations?
Choose the most appropriate number for each situation:

0= would never fall asleep
1= slight chance of falling asleep
2= moderate chance of falling asleep
3= high chance of falling asleep

Activity	Score
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (theater, meeting, etc.)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting quietly after lunch without alcohol	_____
Sitting and talking to someone	_____
In a car, while stopped for a few minutes in traffic	_____
Total	_____

The normal range is generally accepted to be zero to 10.

Multivariable Apnea Prediction (MVAP) Index

"During the last month, have you had, or have been told about the following symptom"
(0) Never;
(1) Rarely, Less Than Once a Week;
(2) 1-2 Times Per Week;
(3) 3-4 Times Per Week;
(4) 5-7 Time Per Week
(.) Don't Know

Symptoms:

- Loud snoring
- Breathing cessation
- Snorting or gasping

Index 1 is the average of the 3 symptom scores.

The estimated probability that a patient will have an RDI ≥10 is:
Probability = ex/(l + ex)
where
x = -8.160 + 1.299-Index I + 0.163-BMI - 0.028-Index I-BMI + 0.032-Age + 1.278-Male,
and Male = 1 if male and 0 if female.

Appendix C. Excluded Studies

X1: Non-English
X2: Ineligible publication type
X3: Ineligible study design
X4: No relevant outcome reported
X5: Poor quality
X6: Superseded by other included article
X7: Abstract only
X8: Ineligible population
X9: Ineligible test or intervention
X10: Ineligible or no comparator
X11: Title
X12: Ineligible country
X13: Full reference inaccessible
X14: Non-surgical intervention in lab setting
X15: Article retracted

1. Continuous positive airway pressure (CPAP) in sleep apnea syndrome - primary research (Structured abstract). Health Technology Assessment Database. 1999(3)PMID: HTA-32000000072. Exclusion Code: X1
2. Summaries for patients. Treatment for sleep apnea in people without symptoms. Ann Intern Med. 2001;134(11):S-8. PMID: CN-00348449. Exclusion Code: X2
3. Polysomnography in patients with obstructive sleep apnea: an evidence-based analysis (Structured abstract). Health Technology Assessment Database. 2006(3):37. PMID: HTA-32006000879. Exclusion Code: X2
4. Value of mandibular advancement devices in cases of obstructive sleep apnea-syndrome (Structured abstract). Health Technology Assessment Database. 2007(3)PMID: HTA-32007000211. Exclusion Code: X1
5. Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome (Structured abstract). Health Technology Assessment Database. 2008(3)PMID: HTA-32011000399. Exclusion Code: X3
6. Continuous positive airways pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome (Structured abstract). Health Technology Assessment Database. 2008(3)PMID: HTA-32008100157. Exclusion Code: X3
7. A randomised controlled trial of continuous positive airway pressure treatment in older people with obstructive sleep apnoea hypopnoea syndrome (PREDICT) (Project record). Health Technology Assessment Database. 2010(3)PMID: HTA-32010000363. Exclusion Code: X2
8. Pre-operative screening and post-operative monitoring in adult patients with obstructive sleep apnea: clinical effectiveness and guidelines (Structured abstract). Health Technology Assessment Database. 2010(3)PMID: HTA-32011001187. Exclusion Code: X3
9. An assessment of sleep disordered breathing diagnosis using Level I versus Level III sleep studies (Structured abstract). Health Technology Assessment Database. 2010(3)PMID: HTA-32013000161. Exclusion Code: X3
10. Rehabilitation Program as an Alternative Therapy for Moderate to Severe Obstructive Sleep Apnea Syndrome. 2011. Exclusion Code: X4
11. Level I and level III sleep studies for the diagnosis of Sleep Disordered Breathing (SDB) in adults (Project record). Health Technology Assessment Database. 2013(3)PMID: HTA-32013000133. Exclusion Code: X3
12. GLYCOSA Study:Effect of PAP Treatment on Glycemic Control in Patients With Type 2 Diabetes. 2013. Exclusion Code: X5
13. Continuous Positive Airway Pressure (CPAP) in Patients With Acute Coronary Syndrome and Obstructive Sleep Apnea (OSA). 2014. Exclusion Code: X4

14. RCT of the Effect of Uvulopalatopharyngoplasty Compared to Expectancy in Patients With Obstructive Sleep Apnea. 2014. Exclusion Code: X4
15. Corrections to Continuous positive airway pressure in older people with obstructive sleep apnoea syndrome (PREDICT): Aa 12-month, multicentre, randomised trial [Lancet Respir Med, 2, (2014), 804-812]. Lancet Respiratory Medicine. 2014;2(11):e22. PMID: CN-01038283. Exclusion Code: X2
16. Comparative Effectiveness Research to Enhance Outcomes in African-Americans With Obstructive Sleep Apnea. 2014. Exclusion Code: X4
17. Obstructive Sleep Apnea (OSA), Sleepiness, and Activity in Diabetes Management. 2014. Exclusion Code: X4
18. Effects of Treating Obstructive Sleep Apnea in Epilepsy. 2014. Exclusion Code: X6
19. Lifestyle Modification Program to Treat Obstructive Sleep Apnea Patients. 2015. Exclusion Code: X5
20. Diagnosis, Cost and Therapeutic Decision-Making of Home Respiratory Polygraphy for Patients Without High Suspicion of OSA or With Comorbidity - Hospital Polysomnography in Comparison With Three Nights of Home Respiratory Polygraphy. 2015. Exclusion Code: X8
21. Aaronson JA, Nachtegaal J, van Bezeij T, et al. Can a prediction model combining self-reported symptoms, sociodemographic and clinical features serve as a reliable first screening method for sleep apnea syndrome in patients with stroke? Arch Phys Med Rehabil. 2014 Apr;95(4):747-52. Epub: 2014/01/01. PMID: 24378806. Exclusion Code: X3
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28. ACTRN12608000301369. Metabolic and Neurobiological changes after Continuous Positive Airway Pressure treatment for Obstructive Sleep Apnea. 2015. Exclusion Code: X4
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Appendix D Table 1. Quality Ratings of Studies of Screening Questionnaires and Clinical Prediction Tools (KQ 2)

First Author, Year	Test(s) adequately described (or referenced)?	Was the spectrum of patients representative of the patients who will receive the test in PC?	Were selection criteria clearly described?	Did the whole or a random selection of the sample receive reference test?	Did patients receive the reference test (and the same reference test) regardless of screening test results?	Was the reference standard independent of the test?	Were the index test and reference standard results interpreted independently blinded (each test interpreted blinded to the result of the other)?	Were withdrawals from the study explained (post-enrollment)?	Were methods for calculating accuracy clearly reported and valid?
Gurubhagava-tula, 2013[104]	Yes	Partially; sample was 80% men, had higher prevalence of any OSA (AHI ≥5 for 80%; and mean AHI of 22.5) than would be expected, age limited to 30-65, and had high proportion of African Americans (59%); they enrolled consecutive outpatients with HTN aged 30-65; some from HTN clinic.	Yes	No, all were invited for PSG, but 21% (52/250) did not get it	Yes	Yes	Yes	Partially	Yes
Morales, 2012[103]	Yes	Partially; sample was ≥65, had higher prevalence of sleepiness than would be expected (74% reported that they had a problem staying awake every day or several [≥3] days per week; 32% had ESS >10)	Yes	No, all were invited but 19% (104/556) of all those screened did not get it; some of those were ineligible—roughly 13% of those eligible did not complete studies	Yes, and they sought to recruit equal numbers of study participants for each decile of MAP score	Yes	Yes	Yes	Yes
Hrubos-Strom, 2011[102]	Yes	Yes, for the screening sample; but, not for the clinical sample—the sample who had PSG oversampled the high-risk group,	Yes	No, 1772 (of 9319 eligible for random draws) were randomly drawn. Of those 1772, 518 (29%) had PSG; the	No	Yes	Yes	Yes	Yes

Appendix D Table 1. Quality Ratings of Studies of Screening Questionnaires and Clinical Prediction Tools (KQ 2)

First Author, Year	Test(s) adequately described (or referenced)?	Was the spectrum of patients representative of the patients who will receive the test in PC?	Were selection criteria clearly described?	Did the whole or a random selection of the sample receive reference test?	Did patients receive the reference test (and the same reference test) regardless of screening test results?	Was the reference standard independent of the test?	Were the index test and reference standard results interpreted independently blinded (each test interpreted blinded to the result of the other)?	Were withdrawals from the study explained (post-enrollment)?	Were methods for calculating accuracy clearly reported and valid?
		had higher ESS scores, rates of snoring		sample of 518 overrepresented the BQ high risk group					
Gurubhagava-tula, 2004[105]	Yes	No, commercial drivers, 93.5% men, 85% white, and oversampled the higher-risk group (247 of the 406 who had PSG)	Yes	No, sampling strategy was to invite all of those with the highest risk scores and then a random (and smaller) sample of the lower-risk group	No, sampling strategy was to invite all of those with the highest risk scores and then a random (and smaller) sample of the lower-risk group	Yes	Yes	Yes, to some degree	Yes

Abbreviations: AHI=apnea-hypopnea index; ESS=Epworth Sleepiness Scale; HTN=hypertension; MAP=multivariate apnea prediction; OSA=obstructive sleep apnea; PC=primary care; PSG=polysomnography.

Appendix D Table 2. Quality Ratings for Studies of Screening Questionnaires and Clinical Prediction Tools for KQ2

First Author, Year	Did the study have high attrition raising concern for bias?	Equal, valid, reliable ascertainment of exposure/ risk factors?	Were outcome assessors masked to risk factors?	Was an appropriate method used to handle missing data?	Did the study use acceptable statistical methods?	Was the sample size adequate to detect differences?	Quality	Comments
Gurubhaga-vatula, 2013[104]	Yes, 21% (52/250) did not have PSG; 23% (58/250) did not have adequate home sleep test	Yes (self-report for age, sex; BMI was measured)	Yes	Yes, multiple imputation	Yes	Unclear; no sample size calculation	Fair	Some concern for attrition bias (although they used good methods for handling missing data) and for selection bias and spectrum bias (with high prevalence of OSA)
Morales, 2012[103]	No	Yes	Yes	Yes	Yes	Unclear; no sample size calculation	Fair	Some concern for selection bias and spectrum bias (with high prevalence of sleepiness)
Hrubos-Strom, 2011[102]	Yes, 518/1772 (29%) subjects randomly drawn had PSG; 518/1350 (38%) invited by mail for PSG had it	Yes	Yes	Yes; 1 or more items were missing on 43.8% of BQs; Zeros were imputed for missing data on BQs, but they conducted sensitivity analysis using maximum values (doing so did not significantly change the results)	Yes	Unclear, no sample size calculation	Fair	Moderate concern for attrition bias, spectrum bias (oversampling of high-risk subjects), and missing data; however, would expect those biases to favor the accuracy of BQ—and this study did not find good accuracy
Gurubha-gavatula, 2004[105]	Yes, less than half of those in the high-risk group invited for PSG attended (247/551); unclear how many were invited from the 778 lower-risk group to get 159 to attend PSG	Yes	Yes for symptoms and questionnaires; unclear for BMI and sex (seems they were observing the PSG and may have ascertained these)	Unclear if anything was done	Yes	Unclear, no sample size calculation	Poor	High risk of selection bias; high risk of attrition bias and spectrum bias (oversampling of high-risk subjects); unclear handling of missing data

Abbreviations: BMI=body mass index; BQ=Berlin Questionnaire; NR=not reported; OSA=obstructive sleep apnea; PSG=polysomnography.

Appendix D Table 3. Quality Ratings of Systematic Reviews and Meta-Analyses for KQ 3

First Author, Year	Was the review based on a focused question of interest?	Was the literature search strategy clearly described?	Was there evidence of a substantial effort to search for all relevant research?	Were there explicit inclusion/ exclusion criteria for the selection of studies?	Did at least 2 people independently review studies?	Was the validity of included studies adequately assessed?	Was publication bias assessed?	Was heterogeneity assessed and addressed?	Was the approach used to synthesize the information adequate and appropriate?	Were the authors' conclusions supported by the evidence they presented?	Quality Rating
Balk, 2011[1]	Yes	Yes	Yes	Yes	Yes	Yes	Partially (Low/ inadequate strength of evidence,	Yes (Statistical testing, subgroup analyses)	Yes	Yes	Good
El Shayeb, 2014[112]	Yes	Yes (Appendix 1)	Yes (2004-March 2013)	Yes (Appendix 2)	Yes	Yes (QUADAS-2)	Partially (Grey literature in Appendix 1, contacted experts)	Yes (Subgroup analyses, sensitivity analyses)	Yes	Yes	Good

Abbreviations: QUADAS-2=Quality Assessment of Diagnostic Accuracy Studies 2.

Appendix D Table 4. Quality Ratings of Newly Identified Included Studies for KQ 3

First Author, Year	Were the tests adequately described (or referenced)?	Were selection criteria clearly described?	Is the time period between the test (PM) and reference test (PSG) short enough (to be reasonably sure that the condition did not change between the 2 tests)?	Did the whole or a random selection of the participants receive the reference test (PSG)?	Did patients receive the reference test (and the same reference test) (PSG) regardless of screening test results?	Was the reference standard independent of the test?	Were the test (PM) and reference standard (PSG) results interpreted independently (blinded)?
Alvarez, 2009[126]	Yes	Yes	Yes	Yes	Yes	Yes	NR
Alvarez, 2012[118]	Yes	Partially	Yes	Yes	Yes	Yes	Yes
Barak-Shinar, 2013[115]	Yes	Yes	Yes	Yes	Yes	No	Yes
Bohning, 2011[121]	Partially	Partially	Yes	Yes	Yes	Yes	Yes
Bruyneel, 2011[110]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Campbell, 2011[111]	Yes	Yes	Yes	Yes	Yes	Yes	No
Choi, 2010[125]	Yes	Yes	Yes	Yes	Yes	Yes	NR
Ferre, 2012[109]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Garg, 2014[127]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Guerrero,2014[113]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gurubhagavatula, 2013[104]	Yes	Yes	NR	Partially	Yes	Yes	Yes
Masa, 2011[119]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Morillo, 2013[116]	Yes	Yes	Yes	Yes	Yes	No	NR
Nigro, 2010[124]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nigro, 2013[117]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pereira, 2013[114]	Yes	Partially	Yes	Yes	Yes	Yes	Yes
Poupard, 2012[120]	Yes	Yes	Yes	Yes	Yes	Unclear	NR
Rofail, 2010[122]	Yes	Yes	Partially	Yes	Yes	Yes	Yes
Yadollahi, 2010[123]	Yes	Partially	Yes	Yes	Yes	Yes	NR

Abbreviations: NR=not reported; PM=portable monitor; PSG=polysomnography.

Table D5. Quality Ratings of Newly Identified Included Studies for KQ 3

First Author, Year	Were withdrawals from the study explained (post-enrollment)?	Were methods for calculating accuracy clearly reported and valid?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Quality	Comments
Alvarez, 2009[126]	NA	Yes	No	NR	Good	Information on blinding of scoring was not presented. There were no withdrawn patients but authors did not describe whether all data were collected or if there were technical issues resulting in missing data. Cross-validation was performed for the ROC analyses.
Alvarez, 2012[118]	NA	Yes	No	NA	Fair	Selection criteria were not clearly described. Authors report that subjects were included who were suspected of having OSA based on clinical features. Clinical features were not described.
Barak-Shinar, 2013[115]	NA	Yes	No	NR	Fair	The PSG and PM were not independent. Datasets were obtained for all participants, but authors did not describe missing data points or channel failures during the PSG/PM test.
Bohning, 2011[121]	Partially	Yes	No	No	Fair	Patients were screened using cardiorespiratory polygraphy and referred to the sleep lab for further testing. Patients underwent PSG and PM simultaneously and results were independently evaluated. It appears only one person was missing PM data and dropped from analysis. Reported results for Groups 0 and 1 versus 2 and 3 don't appear to be valid given text and counts in Table 1.
Bruyneel, 2011[110]	Yes	Yes	No	No	Fair	PM at home was within 2 weeks of PSG. Authors described 2 patients who did not complete both tests. Authors described the failure rate and reasons of both the PSG and PM. In total, 6% of enrolled participants did not provide complete data. Authors only performed a complete case analysis. Moderate sample size.
Campbell, 2011[111]	Yes	Yes	No	Partially	Fair	PM at home was within 2 weeks of PSG. Authors evaluated PSG on two nights rather than one and confirmed reliability; laboratory night 1 was later described as an adaptation night; it was not immediately clear that laboratory night 2 provided the results for comparison with PM. Only 2 patients had failed PM recordings; technical problems were described well. Patients with failed recordings were dropped from analysis; all others with technical issues were deemed clinically acceptable. Sample

Table D5. Quality Ratings of Newly Identified Included Studies for KQ 3

First Author, Year	Were withdrawals from the study explained (post-enrollment)?	Were methods for calculating accuracy clearly reported and valid?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Quality	Comments
						size is small. Scorer was not blind to PSG vs. PM due to how sound was recorded.
Choi, 2010[125]	No	Yes	No	No	Fair	It is unclear whether the PM and PSG results were interpreted independently. However, the tests were completed in different settings at different times and the PM scoring was automatic (versus manual for the PSG). The overall sample is small (26); two subjects did not successfully undergo portable monitoring (one due to battery failure, one cause unknown) and were excluded from the analysis. This is a narrow spectrum of patients- primarily Korean men presenting with symptoms suggesting OSA- that may prevent generalizability to the US population.
Ferre, 2012[109]	NA	Yes	No	NA	Good	Authors only reported on the 68 patients who completed the protocol.
Garg, 2014[127]	Yes	Yes	No	NR	Good	One participant did not complete the in-lab PSG and PM session and two participants did not complete the at-home PM session. It is unclear what the overlap is among those participants. Authors did not report how missing participant data were handled; it is assumed they were dropped from the analysis.
Guerrero,2014[113]	Yes	Yes	No	NR	Good	Authors provided detailed description of inclusion and exclusion criteria. PSG and PM evaluated within same week; PM used over 3 nights and assessed for consistency. PSG and PM scored manually, separately, and blinded by independent techs. Authors don't describe method of dealing with missing data, but only 1 patient did not have valid PM results.
Gurubhagavatula, 2013[104]	Partially	Yes	Yes	Yes	Fair	Patients underwent in-home PM first and then in-lab PSG; days between events was not reported. Though a large subset of enrolled patients underwent PM and PSG, it is not clear what the overlap is. Authors do not report reasons for patients not undergoing PSG and/or PM, but do explain failure rate of studies applied. Missing data, including PSG and PM AHI were imputed, but only a reference was provided for the method. 21% of

Table D5. Quality Ratings of Newly Identified Included Studies for KQ 3

First Author, Year	Were withdrawals from the study explained (post-enrollment)?	Were methods for calculating accuracy clearly reported and valid?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Quality	Comments
						enrolled participants declined PSG and 17% of enrolled participants declined PM so there is a concern for selection bias.
Masa, 2011[119]	Yes	Yes	No	No	Good	Although authors did not use any methods for handling missing data, overall attrition was very low (5%) and unlikely to bias results.
Morillo, 2013[116]	NA	Yes	No	NR	Fair	A convenience sample of 115 consecutively referred patients comprised the participant population; none were excluded post-enrollment. A sleep specialist analyzed the complete set of recordings from the PSG; output from the pulse oximeter (which was part of the PSG) appear to have been downloaded and automatically scored/analyzed according to the multivariate features extraction methods described by the authors but it remains unclear if analyst interpreted results independently. Authors did not describe missing data from the PSG or pulse oximeter.
Nigro, 2010[124]	Yes	Yes	Partially	No	Fair	Ten of 76 (13%) patients were dropped from the analysis, 1 out of choice and 9 because of technical problems with the PSG or PM. Technical difficulties may be related to disease severity, leaving some concern for bias.
Nigro, 2013[117]	Yes	Yes	No	NR	Good	Authors did not report on any technical issues during PSG/PM in the sleep lab or if there was missing data. However, all other aspects of the study are clearly described and valid.
Pereira, 2013[114]	NA	Yes	No	Yes	Good	Authors describe inclusion and exclusion criteria but do not elaborate on the reason(s) for referral to the sleep disorders clinic. PM nights were completed before the PSG night. The PM was scored manually by an experienced scorer who was blind to the PSG results; the PSG was manually scored by registered PSG techs who were blind to the PM results. The PM was worn on the second night as a backup for the first night; authors reported the first night failure rate.

Table D5. Quality Ratings of Newly Identified Included Studies for KQ 3

First Author, Year	Were withdrawals from the study explained (post-enrollment)?	Were methods for calculating accuracy clearly reported and valid?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Quality	Comments
Poupard, 2012[120]	NA	Yes	No	NA	Fair	Spectrum of patients was unclear; authors report that patients are a referral population for sleep apnea syndrome but do not provide additional details. It is unclear whether the pulse oximetry was independent of the gold standard (versus part of the full PSG monitoring). The authors did not describe whether the oxygen saturation data were blindly scored.
Rofail, 2010[122]	No	Yes	No	Partially	Fair	There was a possibility of up to 8 weeks between PSG and PM evaluations. No explanation was provided for 7 (7%) withdrawn patients. Patients without sufficient data from PSG and/or PMs were dropped from analysis, but authors did average data over 3 nights for the PMs, allowing for more participants to be included.
Yadollahi, 2010[123]	NR	Yes	NR	Yes	Fair	No additional information on the patients already undergoing PSG were provided. Blinding of technicians was not reported. There was a small amount of data missing from the PMs but the authors describe averaging and other adequate approaches to handle the missing data. Authors do not report on withdrawals/attrition.

Abbreviations: AHI=apnea-hypopnea index; NA=not applicable; NR=not reported; OSA=obstructive sleep apnea; PM=portable monitor; PSG=polysomnography; ROC=receiver operating characteristic.

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
Aarab, 2011[189]	Yes	Yes	Yes	Yes	MAD use 91% of nights nCPAP 83% of nights Intraoral placebo device 94% of nights	11%	13% (MAD vs. nCPAP), 5% (MAD vs. Intraoral placebo device) 7% (nCPAP vs. Intraoral placebo device)	Partially	No
Andren, 2013[188]	Yes	NR	Mostly	Yes	NR	1%	3%	No	No
Arias, 2005[128]	NR	NR	Yes (cross-over study)	NA	7% were nonadherent (use <3.5 hrs/night) and excluded from analysis; of the rest: CPAP: 6 hrs/night; sham 6 hrs/night	7%	7%	No	No
Arias, 2008[129]	NR	NR	Yes	NA	CPAP: 6.2 hrs/night Sham CPAP: 6.3 hrs/night	17%	Unclear	Unclear (unable to determine differential attrition)	No
Bäck, 2009[198]	Yes	Yes	Yes	NA	NA	0%	0%	No	No
Ballester, 1999[170]	NR	NR	Yes	NA	Mean CPAP 5.2 hrs/night; 73% used it >4.5 hrs/night	0%	0%	No	No
Barbe, 2001[130]	Yes	NR	Yes	NA	CPAP: 5 hrs/night; Sham: 4 hrs/night	2%	2%	No	No
Barbe, 2010[171]	Yes	Yes	Mostly	NR	CPAP: mean use 4.7 hrs/night	4%	6%	No	No
Barbe, 2012[172]	Yes	Yes	Yes, although AHI was a little higher in CPAP group	NA	CPAP: median 5h/night; 36% with mean use <4h per night	Loss to follow-up: 17%	1%	No	No

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
Bardwell, 2007[131]	NR	NR	Partially (SaO2 different)	NA	CPAP: 6.3 hrs/night; Sham CPAP: 6.0 hrs/night	0%	0%	No	No
Barnes, 2004[173]	Yes	Yes	Yes	NA	CPAP: 3.6 hrs/night; MAD: 5.5 hrs/night; Placebo: 94.3%	23%	6%	Yes, high overall	No
Bloch, 2000[214]	Yes	NR	Yes (cross-over study)	NA	MADs: at least 4 to 7 nights/week No tx: NA	0%	NA	No	No
Browaldh, 2013[199] SKUP3	Yes	Yes	Yes	NA	NA	8%	NR	No	No
Campos-Rodriguez, 2006[132]	NR	Unclear	Yes	NA	5.0 vs. 4.4 hrs/day for CPAP vs. sham	6%	0%	No	No
Chasens, 2014[287]	Yes	NR	Partially	NA	74% were adherent for at least 4 hours per night	4.3%	9%	No	No
Chong, 2006[134]	NR	No	Yes	NA	5.2 hrs/night	5%	0%	No	No
Coughlin, 2007[135]	Yes	NR	Yes (cross-over)	NA	CPAP: 3.9 hrs/night; Sham CPAP: 2.6 hrs/night	3%	0%	No	No
Craig, 2012[174] MOSAIC	Yes	Yes	Yes	NA	Median CPAP usage: 2.39 h/night (IQR: 0.36 to 4.59)	13% for the coprimary outcome ESS (lower for some secondary outcomes)	0%	No	No
Cross, 2008[136]	NR	NR	Yes (cross-over study)	NA	CPAP: 4.5 hrs/night; Sham: 3.1 hrs/night	17%	4%	No	No

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
Desplan, 2014[204]	NR	NR	ESS scores and BP higher in intervention group	NR	NR (but inpatient program, so implied to be 100% for the completers)	15%	0	No	No
Dixon, 2012[200]	NR	NR	Yes	Yes (for surgical group); NR for weight loss group	13% of the surgical group did not consent to surgery; adherence to weight loss intervention NR; CPAP adherence was about 67% for both groups	Non-completers: 10% for main outcomes, 13% for QOL outcomes; Loss to follow-up 0%	7% (for main outcomes; unclear for QOL outcomes	No	No (small number of cross-overs)
Durán-Cantolla, 2010[137]	Yes	Yes	Yes	NA	Mean 4.2 (Sham) to 4.5 (CPAP) hrs/day over 12 weeks; 59% (Sham) and 65% (CPAP) used >4 hours/day	20% did not complete the trial (either refused to continue, intolerant to CPAP, protocol violation, or technical problems)	2%	Borderline for overall attrition; no for differential attrition	No
Durán-Cantolla, 2015[36]	Yes	Yes	NA (cross-over)	NA	MAD: 6.4 hrs/night; placebo: 6.2 hrs/night	10%	5%	No	No
Egea, 2008[138]	NR	NR	Yes based on N randomized, but partially based on N analyzed	NA	NR	18%	4%	No	No

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
Engleman, 1994[216]	NR	NR	Yes	NA	CPAP: mean 3.7 hrs/night	9%	Unclear	No	No
Engleman, 1997[217]	NR	NR	Yes	NA	CPAP mean 3.2 hrs/night	11%	20%	Partially	No
Engleman, 1998[175]	NR	NR	Yes	NA	Mean of 3.2 hours of CPAP runtime and used effectively 2.8 hours per night	0%	0%	No	No
Engleman, 1999[176]	NR	NR	Yes	NA	CPAP 3.5 hrs/night	8%	NR (at most 8%)	No	No
Faccenda, 2001[177]	NR	NR	Yes (cross-over study)	NA	47% of patients used CPAP at least 3.5 hrs/night; mean use 3.3 hrs/night; placebo adherence almost 100%	4%	2%	No	No
Ferguson, 2003[201]	Yes	NR	Yes	NA	NA (surgery vs. no treatment)	4%	4%	No	No
Foster, 2009[205] Kuna, 2013[206] Sleep AHEAD	Yes	Yes	Yes	NA	NR	At 1 yr: 17% At 2 yrs: 20% At 4 yrs: 38%	At 1 yr: 1% At 2 yrs: 1% At 4 yrs: 6%	At 4 yrs, high overall	No
Gottlieb, 2014[178] HeartBEAT	Yes	Yes	Partially	NA	CPAP: 3.5 hrs/night Oxygen: mean 4.8 hrs/night	12% for primary outcome; 5% to 7% for other outcomes	3% to 7%	No	No
Haensel, 2007[139]	NR	NR	Yes	NA	CPAP: 6.6 hrs/night; Sham CPAP: 6.0 hrs/night	0%	0%	No	No

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
Hoyos, 2012[140]	Yes	Yes	Yes	NA	CPAP: 3.6 hrs/night; Sham CPAP: 2.8 hrs/ night	Loss to followup at 12 weeks: 20%; Missing data for ESS and BP: 23%	11% (from published correction); 2% (from Table 2)	Yes	No
Hui, 2006[141]	NR	NR	Yes	NA	CPAP 5.1 hrs/night; sham 2.6 hrs/night	18%	0%	No	No
Ip, 2004[179]	NR	NR	Yes	NA	CPAP: 4.3 hrs/night UC: NA	4%	4%	No	No
Jenkinson, 1999[142] Hack, 2000[143]	NR	Yes	Yes	NA	CPAP 5.4 hrs/night; sham 4.6 hrs/night	6%	4%	No	No
Johansson, 2009[207]	Yes	Yes	Yes	NA	VLCD: 100%	3%	6%	No	No
Johnston, 2002[195]	NR	NR	Yes	NA	MAD 68% every or almost every night; 79% ≥4 hrs/night	5%	5%	No	No
Jones, 2013[144]	Yes	NR	Yes	NA	CPAP: 3.0 hrs/night Sham CPAP: 2.0 hrs/night	19%	5%	No	No
Kline, 2012[208] Kline, 2013[209]	Yes	Yes	Partially (exercise training group had higher mean AHI (32 vs. 24), higher mean baseline weight and BMI, higher percentage	NA	Rate of attendance 87% (exercise) 79% (control); 81% of the treatment group received the targeted aerobic dose	12% (non-completers)	2%	No	No

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
			White, lower percentage with prior OSA treatment)						
Koutsourelaski, 2008[202]	Yes	NR	Yes	NA	NA (surgery)	0%	0%	No	No
Kushida, 2012[145] Batool-Anwar, 2016[288]	Yes	Yes	Yes	NA	CPAP: 5.8 hrs/night Sham: 4.3 hrs/night	23% (for ESS at 6 months; varies by outcome and timing)	5%	Yes	No
Lam, 2007[180]	Yes	NR	Yes	NA	CPAP: 4.2 hrs/night; MAD: 6.4 hrs/night	10%	3% to 12%	Partially	Partially
Lam, 2010[146]	Yes	NR	Yes	NA	CPAP 6.2 hrs/night; sham 4.5 hrs/night	0%	0%	No	No
Lee, 2011[147]	NR	NR	Yes	NA	CPAP: 5.0 hrs/night; Placebo CPAP: 6.9 hrs/night	NR, presume 0	NR, presume 0	No	No
Lim, 2007[215]	NR	NR	Yes	NA	NR	0	0	No	No
Loredo, 1999[148]	NR	NR	Partially (RDI higher in CPAP than pbo)	NA	Both groups: >5 hrs/night	15%	Somewhat unclear (if 48 randomized resulted in 24 in each group, then 21%, 12%, and 16%, respectively	Somewhat unclear due to limited reporting	No
Loredo, 2006[149]	NR	NR	Yes	NA	CPAP: 6.6 hrs/night Sham CPAP: 6.0 hrs/night	Unclear which exclusions were prior to vs. after	NR	No for overall; unclear for differential	No

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
						randomiz-ation (max would be 17%)			
Malow, 2008[150]	Yes	Yes	Yes	NA	CPAP: 4.7 hrs/night Sham CPAP: 3.6 hrs/night	9%	14%	Yes; all noncompleters were from G1; 9% of G1 d/c due to inability to tolerate CPAP—maybe higher severity?	No
Marshall, 2005[151]	Yes	Yes	Yes (cross-over study)	NA	CPAP: 4.9 hrs/night; Sham CPAP 4.9 hrs/night	7%	<1%	No	No
Martinez-Garcia, 2013[181] HIPARCO	Yes	Yes	Yes	NA	CPAP: 5 hrs/night; 72% at least 4 hours/night	10%	2%	No	No
McArdle, 2001[152]	Yes	Yes	NA (cross-over)	NA	Median 4.5 hrs/night	4%	4%	No	No
McMillan, 2014[182] PREDICT	Yes	Yes	Yes	Yes	71% reported still using CPAP at 12 mths; at 3 mths, median usage of 1 h 52 min per night; at 12 mth, 2 h 22 min/night	17	3	No	No
Mills, 2006[153]	NR	NR	Partially; 47% HTN in CPAP arm, 25% in sham arm	NA	CPAP: 6.8 hrs/night Sham: 6.0 hrs/night	NR, presume 0	NR, presume 0	No	No

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
Montserrat, 2001[154]	Yes	NR	Partially	NA	CPAP 4.3 hrs/night; sham 4.5 hrs/night	4%	0%	No	No
Moss, 2014[210]	Yes	NR	Yes	NR	Exercise: 96% of sessions attended; control: NA	10%	0%	No	No; all patients were on CPAP for at least 6 months prior
Naismith, 2005;[192] Gotsopoulos, 2002;[193] Gotsopoulos, 2004[194]	Yes	Yes	Yes (crossover study)	NA	Both MAD and sham MAS: 6.7 hrs/night; 96-97% of nights	9%	5%	No	No
Neikrug, 2014[155]	Yes	NR	Yes	NA	CPAP: 5.2 hrs/night	18%	5%	No	No
Nguyen, 2010[157]	NR	NR	Yes	Yes	NR (assessed but not reported)	0%	0%	No	No
Norman, 2006[156]	NR	NR	Partially; higher SBP and MAP in CPAP group	NA	CPAP: 6.7 hrs/night Sham: 6.0 hrs/night	NR, presume 0	NR, presume 0	No	No
Pamidi, 2015[158]	Yes	Yes	Mostly: 19% of CPAP had HTN; 0% of pbo had HTN	NA	8 hrs/night—all CPAP patients slept in the lab and were required to wear CPAP whole night	15%	11%	Borderline for differential	No
Pepperell, 2002[159] Kohler, 2008[160]	NR	NR	Yes	NA	4.9 h/night for CPAP and 4.5h/night for Sham	20% (for missing blood pressure data)	1% (for blood pressure outcomes)	No	No
Petri, 2008[191]	Yes	Yes	Yes	NA	NR	13%	1%-15%	Partially (G1 vs. G3)	No

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
Phillips, 2011[161]	Yes	Yes	Yes	NA	CPAP: 4.4 hrs/night Sham CPAP: 3.4 hrs/night	24%	5%	Yes overall, but not differential	No
Quinnell, 2014[197] TOMADO	Yes	Yes	Yes	NA	Mean (SD) 4.4 (2.4) to 5.7 (2.0) hrs/night for the 3 MAD groups	18% did not complete; 8% not analyzed	Low when comparing most groups, but high for bMAD group vs. others (17%-30% differential)	Yes (high differential attrition for bMAD group compared with the others)	No
Redline, 1998[183]	Yes	NR	Mostly (slightly higher RDI in CPAP arm, and fewer women)	NA	CPAP: 44% of sleep time; 3.1 hrs/night CT: 82% of nights	13%	2%	No	Possibly*
Robinson, 2006[162]	NR	Yes	Yes	NA	CPAP: 5.2 hrs/night; Sham CPAP: 4.3 hrs/night	9%	9%	No	No
Ruttanaumpawan, 2008[184]	NR	NR	Partially; higher AHI in control, but they adjusted for it in analyses	NA	CPAP: 6.2 hrs/night	NR, presume 0	NR, presume 0	No	No
Siccoli, 2008[164]	NR	NR	Yes	NA	CPAP: 4.7 hrs/night Sham CPAP: 3.9 hrs/night	3%	2%	No	Possibly – 52 has been involved in previous study on CPAP effect on BP

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
Smith, 2007[163]	Yes	NR	Yes	NA	CPAP 3.5 hrs/night; Sham 3.3 hrs/night	15%	Unable to determine	No	No
Tomfohr, 2011[186]	NR	NR	Yes	NA	5.5 hrs/night for CPAP group; 6.6 for sham CPAP	17%	4%	No	No
Toukh, 2012[165]	Yes	NR	NA (cross-over)	NA	NR	8%	NR	No	No
Tuomilehto, 2009[211] Tuomilehto, 2010[212] Tuomilehto, 2013[213]	Yes	NR	Partially	NA	NR	At 12 wks: 9% At 1 yr: 11% At 2 yrs: 12% At 5 yrs: 30%	1%-3%	Partially (at 5 yrs)	No
Usui, 2005[187]	NR	NR	Partially: no women in CPAP vs. 29% in control and fewer patients with HTN in CPAP vs. control	NA	NR/NA	NR, presume 0	NR, presume 0	No	No
Weaver, 2012[166]	Yes	Yes	Yes, except slightly higher score on mental health component of SF36 for sham CPAP group	NA	CPAP: 4.0 hrs/night; Sham: 3.1 hrs/night	Overall: 21% who were randomized were not included in analyses (15% withdrew prior to receiving CPAP or sham;	1%	Yes, high overall	No

Appendix D Table 6. Quality Ratings oIncluded Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was intervention fidelity adequate?	What was the reported adherence to the intervention?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?
						another 6% were missing data for the primary outcome)			
Weinstock, 2012[167,289]	Yes	NR	Yes	NA	Mean nightly use: CPAP: 4.8h Sham CPAP: 3.4h; p<00.1	2% (1 participant completed the first [CPAP] period only)	4%	No	No
West, 2007[168] West, 2009[169]	Yes	NR	Yes	NA	CPAP: 3.6 hrs/night Sham CPAP: 3.3 hrs/night	5%	0%	No	No
Woodson, 2003[203]	Yes	Yes	Yes	Good (e.g., planned 5 tongue sessions and delivered 4.5 +/- 0.8)	NA	11%	6%	No	No

*Subjects with symptoms of nasal congestion were provided with a nasal steroid spray, and it's NR whether there was an equal proportion of such patients in each arm. Control pts got nasal dilator strips.

Abbreviations: AHEAD=Action for Health in Diabetes; AHI=apnea-hypopnea index; bMAD=fully-bespoke mandibular advancement device; BMI=body mass index; BP=blood pressure; CPAP=continuous positive airway pressure; ESS=Epworth Sleepiness Scale; G=group; HeartBEAT=Heart Biomarker Evaluation in Apnea Treatment; hrs=hours; HTN=hypertension; IQR=interquartile ratio; MAD=mandibular advancement device; MOSAIC=Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular; mth=month; N=number; NA=not applicable; nCPAP=nasal continuous positive airway pressure; NR=not reported; OSA=obstructive sleep apnea; QOL=quality of life; RDI=respiratory disturbance index; Sa02=oxygen saturation; SBP=systolic blood pressure; SKUP3=Sleep apnoea Karolinska; TOMADO=trial of oral mandibular advancement devices for obstructive sleep apnoea-hypopnoea; tx=treatment; UPPP=uvulopalatopharygoplasty; VLCD=very low calorie diet; vs.=versus.

Appendix D Table 7. Quality Ratings of Studies of Included Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Aarab, 2011[189]	Yes	Partially	NR	NR	Yes	Worst and best case sensitivity analyses	Yes	Fair	Differential attrition between two treatment groups, do not suspect that this contributes to significant bias when both groups are compared to placebo. Only the comparison of the active and "sham" oral device was masked; patients receiving CPAP were not masked.
Andren, 2013[188]	Yes	Yes	NR	Yes (for Ambulatory BP monitoring and AHI); NR for ESS	Yes	BOCF	Yes	Fair	Allocation concealment is not described. Compliance with intervention and control is not described. More patients in the control group were on antihypertensive medications compared to the active treatment group (47% vs. 25%, respectively). Not clear whether changes in antihypertensives were allowed during the trial (and BP measures are the primary outcome)
Arias, 2005[128]	Yes	Yes	NR	NR	Yes	Excluded	Partially	Fair	Excluded non-adherent patients from analysis, but N=2. No description of randomization or blinding of assessors.
Arias, 2008[129]	Yes	Yes	NR	Yes	Yes	Excluded	Other than no handling of missing data, acceptable methods	Fair	Methods of sequence generation and allocation concealment NR; no handling of missing data (not high overall at 17%, but unable to determine differential attrition)
Bäck, 2009[198]	Yes	Yes	No	Partially	Yes	NA	Yes	Good	Some flexibility for outcome timing assessment (4-6 months), but unlikely to have introduced important bias. Surgeon not masked, but not feasible to mask the surgeon. Patients were masked, so self-reported outcomes are blinded; masking of assessors for other outcomes NR. Intended sample size

Appendix D Table 7. Quality Ratings of Studies of Included Randomized, Controlled Trials of Interventions for OSA (KQs 4 and 5)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
									was 34; they randomized 32 (very unlikely to make any difference in their conclusions as they found identical reduction for ESS in both groups, and AHI trend favoring placebo group)
Ballester, 1999[170]	Yes	No	No	No	Yes	NR, but suggests there was no missing data	Yes	Fair	No masking; methods of randomization and allocation concealment NR
Barbe, 2001[130]	Yes	Yes	NR	Yes	Yes	Excluded	Yes	Fair	Methods of allocation concealment NR
Barbe, 2010[171]	Yes	No	NR	NR	Yes	None	Yes	Fair	Differences in baseline AHI and other variables associated with OSA severity (oxygen saturation) were statistically significant but unlikely to be clinically significant. Multiple ROB domains NR. This is a completers' analysis, however overall and differential attrition is low and unlikely to bias results.
Barbe, 2012[172]	Unclear (the composite outcome lumps less severe with more serious outcomes)	No	No	Yes	Yes	None (exposure time ended upon withdrawal or loss to followup)	Yes	Fair	Outcome assessors were masked but statisticians and researchers were not. No sham CPAP (control group received nothing). Could perhaps have improved blood pressure measurement validity/reliability if using 24h ambulatory blood pressure monitoring. Trial may have been underpowered. Some concern with using a composite outcome that combines incidence of HTN with CV events. The latter have a much more significant impact on health and quality of life (and there were few events)

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First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Bardwell, 2007[131]	Yes	Yes	NR	NR	Yes	NA	Unclear	Fair	Not much information on randomization and masking; short duration ok because we are only using the RDI data; not much info on statistical analyses for RDI
Barnes, 2004[173]	Yes	Yes	NR	NR	Yes	Multiple imputation	Yes	Fair	Risk of attrition bias; masking of providers and outcome assessors NR.
Bloch, 2000[214]	Yes	No	NR	NR	Yes	NA	Yes	Fair	Open-label for patients; other masking NR; sequential open-label treatment could bias self-reported outcomes.
Browaldh, 2013[199] SKUP3	Yes	No	No	Partially	Yes	Baseline values +1	Yes	Good	Sleep data assessors were blinded; BMI results were not. Although we're not given the actual results of the ITT analyses, I don't think there's concern for bias.
Campos-Rodriguez, 2006[132]	Yes	Yes	Yes	Yes	Yes	None, excluded	Other than no handling of missing data, acceptable methods	Fair	Methods or generating randomization sequence NR; unclear if allocation concealed (used presealed envelopes, but unclear if the person assigning to treatment groups was the person who knew the sequence and filled the envelopes)
Chasens, 2014[287]	Yes	Yes	NR	No	Yes	NR	Yes	Fair	Very small study (N=23) that aimed to determine feasibility of conducting an RCT of CPAP vs. sham CPAP focused on improving activity; Baseline AHI and oxygen desaturation indexes were higher in the active CPAP group; research staff were masked to group except for the night PSG technician who performed the overnight titration and the study's sleep physician co-investigator

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First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Chong, 2006[134]	Yes	Yes	No	Yes	Yes	NR	NR, unclear if ITT or per protocol analysis; otherwise acceptable	Fair	Methods of randomization NR; lack of allocation concealment. Likely used completers analysis because no description of handling of missing data, but very low attrition (1 person in each group at 3 weeks).
Coughlin, 2007[135]	Yes	Yes	Yes	Yes	Yes	Excluded	Yes	Good	Only 1 person lost/excluded, and since it's cross-over, not a big concern
Craig, 2012 MOSAIC[174]	Yes	No	No	Partially	Yes for the primary outcomes; likely not adequate for some secondary outcomes (e.g., stroke, vascular events)	None for primary outcomes and most secondary outcomes; used multiple imputation for risk score analyses	No, completers analysis (analyzed on ITT basis but excluded those with missing data and those who attended their 6 month visit either more than 4 weeks earlier or 8 weeks later than the expected data)	Fair	Lack of masking (according to the supplemental appendix, "it was not possible to blind all trial staff, although the assessments were done blind whenever possible"); completer's analysis (but not a lot of missing data),
Cross, 2008[136]	Yes	Yes	Yes	Yes	Yes	Excluded	Partially	Fair	Randomization method NR, small N, excluded some dropouts but not all
Desplan, 2014[204]	Yes	No	No	NR	Yes	None, excluded	Other than no handling of missing data, acceptable methods	Fair	

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First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Dixon, 2012[200]	Yes	No	No	Yes for AHI; NR for other outcomes	Yes	Multiple imputation	Yes	Fair	Method of randomization, allocation concealment were not reported. Lack of masking patients and providers (although likely not realistic for this intervention and comparison).
Durán-Cantolla, 2010[137]	Yes	Yes	Yes	Yes	Yes	Baseline observation carried forward	Yes	Good	Although the study had borderline overall attrition, with 20% not completing the 12 week study; they used a conservative BOCF analysis (assuming that blood pressure was not changed from baseline) for people who did not complete. ITT analysis with all randomized subjects. No medications were allowed for hypertension during the study
Durán-Cantolla, 2015[36]	Yes	Yes	Yes	Yes	Yes	NR; looks like excluded	Partially	Good	Small amount of missing data excluded
Egea, 2008[138]	Yes	Yes	NR	Partially	Yes	Excluded	Partially	Fair	Completers analysis, no info on randomization, blinding of outcome assessors other than pts
Engleman, 1994[216]	Yes	Yes	NR	NR	Yes	Excluded from analysis	Yes, other than exclusion of missing	Fair	Self-reported outcome assessors masked b/c patients were masked.
Engleman, 1997[217]	Yes	Yes	NR	NR	Yes	Excluded from analysis	Yes, other than exclusion of missing	Fair for cognitive outcomes poor for ESS	Only 9 of 18 reported ESS, unclear how many from each arm
Engleman, 1998[175]	Yes	Yes	No	NR	Yes	NR	Yes	Fair	Methods of randomization and allocation concealment NR; not clear if outcome assessors masked; approach to missing data NR.

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First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Engleman, 1999[176]	Yes	Yes	NR	Partially	Yes	Excluded	Yes	Fair	Methods of randomization and allocation concealment NR; outcome assessors not masked for some outcomes (patient-reported outcomes masked, others NR).
Faccenda, 2001[177]	Yes	Yes	NR	Yes	Yes	Excluded	Yes	Fair	I consider patients masked because they were told that placebo was beneficial. Poor adherence to CPAP, but analysis of all pts vs. adherent yielded same result for BP; since outcomes were self-reported or via 24-hr BP monitor, I consider outcome assessors masked.
Ferguson, 2003[201]	Yes for valid and reliable; unclear for equal (possible differences in timing of outcome assessment)	No	No	No/NR	Yes	Excluded, completers (and those who refused additional procedures) only	Partially	Fair	Methods of allocation concealment NR; open-label; no masking. Patients in surgery group had multiple procedures until endpoint was reached. LAUP group underwent varying numbers of procedures (mean 2.4). Timing of outcome measurement varied (3 months after last procedure or 6 months after baseline).
Foster, 2009[205] Kuna, 2013[206] Sleep AHEAD	Yes	No	No	Yes	Yes	Mixed-effects MLE and GEE	Yes	Good	High attrition after 2 yrs, but accounted for with statistical methods
Gottlieb, 2014[178] HeartBEAT	Yes	No	Unclear	Yes	Yes	Excluded, though they did multiple imputation sensitivity analyses	Yes	Good	Since all outcomes were objectively recorded, not concerned about lack of blinding causing bias.
Haensel, 2007[139]	Yes	Yes	NR	NR	Yes	NA	Unclear	Fair	No clear method of randomization/allocation; masking NR for providers and assessors—so questionable for AHI (self-report outcomes masked)
Hoyos, 2012[140]	Unclear	Yes	Yes	Yes	Yes	None	No,	Fair	Moderate risk of attrition bias, but it

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							completers analysis		was non-differential for outcomes eligible for our review (ESS, BP); no handling of missing data; completers analysis.
Hui, 2006[141]	Yes	Yes	Yes	Yes	Yes	None, excluded subjects with missing data	No, completers analysis; otherwise acceptable	Fair	Methods of randomization and allocation concealment NR. Completer's analysis introducing some risk of selection bias and confounding. But, low attrition and no differential attrition.
Ip, 2004[179]	Yes	No	No	No	Yes	Excluded	Yes	Fair	Randomization/allocation concealment methods NR; no masking reported (but AHI data may have been automated); no handling of missing data (but only 1 subject without complete data).
Jenkinson, 1999[142] Hack, 2000[143]	Yes	Yes	No	Yes	Yes	None, excluded	Other than no handling of missing data, acceptable methods	Fair	
Johansson, 2009[207]	Yes	No	No	No	Yes	ITT with BL carried forward	Yes	Good for AHI; Fair for ESS	No blinding; not concerned with significant bias for AHI in this study, but potential for bias with the self-reported ESS.
Johnston, 2002[195]	Yes	Yes	NR	NR	Yes	None, excluded	Minimal reporting of methods, completers analysis	Fair	Methods of randomization and allocation concealment NR. Missing data excluded, but little missing data
Jones, 2013[144]	Yes	Yes	Yes	Yes	Yes	Excluded non-completers	Yes	Fair	Inadequate methods of handling missing data, allocation concealment NR

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Kline, 2012[208] Kline, 2013[209]	Yes	No (although both programs were presented as active treat-ments)	No	NR	Yes (for AHI and ESS); unclear for health-related QOL (12 weeks)	LOCF (which is the baseline observation for this study)	Yes	Fair	Baseline age, sex, and education were similar, but some baseline differences for AHI (higher in the intervention group: 32.2 vs. 24.4) and weight; therefore some concern for selection bias. Lack of masking.
Koutsourelaski2008[202]	Yes	Yes	No	Yes	Yes	NA	Yes	Fair	Allocation concealment NR, otherwise this would be good.
Kushida, 2012[145] Batool-Anwar, 2016[288]	Yes	Yes	Yes	Yes	Yes	None	Yes	Fair	High overall attrition; no imputation was performed except for the analysis of adherence, where one version imputed missing values to zeros; analyses used GEE, GLM, or GLMM approaches.
Lam, 2007[180]	Yes	No	No	NR	Yes	Missing values replaced by baseline values	Yes	Fair	Many but not all subjects were referred to a weight-loss program; NR which proportion in each arm; contamination possible. Since more patients withdrew from control arm vs. CPAP and BL values were imputed, it could bias the result against the null. Not a much concern about MAD vs. control; similar rates of attrition.
Lam, 2010[146]	Yes	Yes	Yes	NR	Yes for AHI; unclear for ESS and BP	NA, no missing values for outcomes of interest	Yes	Fair	Methods of allocation concealment NR; unclear if outcome assessors were masked; only 1 week of followup (focus was on insulin sensitivity measures, but they also report AHI, ESS, and blood pressure)

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First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Lee, 2011[147]	Yes	Yes	Yes	Yes	Uncertain	NA	Yes	Fair	No mention of how patients were randomized. CPAP group was less compliant than the sham CPAP group. Uncertain if 3 wks is long enough for cognitive changes.
Lim, 2007[215]	Yes	Yes	Yes	Yes	Unclear	NA	Yes	Fair	Information on methods of randomization and allocation concealment was not described. Compliance with CPAP and sham CPAP was not described. The authors note that 2 weeks may not be sufficient time to assess for improvements in some neurocognitive measures.
Loredo, 1999[148]	Yes	Yes	NR	NR	Yes	Excluded, completers only	Partially	Fair	Methods of randomization, allocation concealment and masking of providers and outcome assessors NR; no handling of missing data.
Loredo, 2006[149]	Yes	Yes	Yes	Yes	Yes	Excluded	Other than no handling of missing data, acceptable methods	Fair	Methods of randomization and allocation concealment NR. Ns randomized are NR, and thus attrition rates by group are unclear (but max overall attrition was 17%, depending on whether some of the exclusions were pre- or post-randomization. Missing data excluded from analysis; completers only.
Malow, 2008[150]	Yes	Yes	Yes	Yes	Yes	Excluded	Partially	Fair	Only usable outcome in this study is AHI, and it's only at 2 nights; pilot/feasibility study not designed to examine efficacy
Marshall, 2005[151]	Yes	Yes	Yes	Yes	Yes	Excluded	Partially	Good	Excluded non-adherent patients from analysis, but N=2. Adjusted appropriately.

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Martinez-Garcia, 2013[181] HIPARCO	Yes	No	No	No	Yes	Multiple imputation	Yes	Good	Since all outcomes were objectively recorded, not concerned about lack of blinding causing bias.
McArdle, 2001[152]	Yes	Yes	NR	Yes	Yes	NR	Mostly	Fair	Very small sample size; missing data excluded
McMillan, 2014[182] PREDICT	Yes	Yes	No	Yes	Yes	Sensitivity analyses with multiple imputation	Yes	Good	
Mills, 2006[153]	Yes	Yes	NR	NR	Yes	NA	Yes	Fair	Much higher %age of HTN in CPAP arm (and pts were tapered off BP meds), not clear if adjusted for this; however, this would bias toward the null, so not a big concern. However, randomization, allocation, and blinding NR. Not explicitly stated that no pts dropped out, but maybe none did.
Montserrat, 2001[154]	Yes	Yes	NR	Yes	Yes	None, excluded	Other than no handling of missing data, acceptable methods	Fair	Methods of allocation concealment NR; excluded dropouts, but just 1 in each group.
Moss, 2014[210]	Yes	No	No	No	Yes	NR; looks like excluded	Other than no handling of missing data, acceptable methods	Fair	
Naismith, 2005;[192] Gotsopoulos, 2002;[193] Gotsopoulos, 2004[194]	Yes	Yes	Yes	Yes	Yes	Conducted both ITT and completers	Yes	Good	

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Neikrug, 2014[155]	Yes	Yes	No	Yes	Yes	None, excluded	Other than no handling of missing data, acceptable methods	Fair	
Nguyen, 2010[157]	Yes	Yes	NR	Yes	Yes	NA	NR	Fair	Multiple ROB domains NR (e.g., randomization, allocation concealment, and adherence).
Norman, 2006[156]	Yes	Yes	NR	NR	Yes	NA	Yes	Fair for AHI; Poor for blood pressure	Methods of random sequence generation and allocation concealment NR; masking of outcome assessors NR; some baseline differences between groups (with higher SBP and MAP in CPAP group—although they adjusted for this in analyses, the baseline SPB of 135 (CPAP) vs. 122 (placebo) indicates that randomization may not have been effective in this small study (15 subjects in placebo group and 18 in CPAP group), and the results might be completely explained by regression to the mean as the groups had almost identical post-treatment BPs. High risk of selection bias and confounding for the blood pressure outcomes.
Pamidi, 2015[158]	Yes	Yes	No	NR	Yes	Sensitivity analyses with imputation	Yes	Fair	Borderline differential attrition, potentially important differences at baseline
Pepperell, 2002[159] Kohler, 2008[160]	Yes	Yes	Yes	Yes	Yes	BOCF (assumed no change in BP for missing)	Yes	Fair	Methods of sequence generation and allocation concealment NR (they used presealed and numbered envelopes, but NR whether the nurse who assigned groups filled the envelopes)

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Petri, 2008[191]	Yes	Yes (G1 vs. G2) No (G1 vs. G3)	Yes (G1 vs. G2) No (G1 vs. G3)	Yes (G1 vs. G2) No (G1 vs. G3)	Yes	Sensitivity analyses with different scenarios	Partially	Fair	Active vs. sham MAD was triple-masked; no masking in the "no treatment" arm. Not concerned about the small amount of cross-over (2 total subjects) and that would bias results toward null (not in favor of the MAD). Missing data handled by use of sensitivity analyses, but they don't present those results.
Phillips, 2011[161]	Yes	Yes	Yes	Yes	Yes	Excluded; completers only	Other than no handling of missing data, acceptable methods	Fair	24% overall attrition (but low differential attrition); no handling of missing data
Quinnell, 2014[197] TOMADO	Yes	No	No	Yes for AHI; unclear for other outcomes	Yes	None, excluded	Other than no handling of missing data, acceptable methods	Fair	Open-label trial; high differential attrition between some groups (but overall attrition and missing data was not high)
Redline, 1998[183]	Yes	No	NR	NR	Yes	Excluded but examined in sensitivity analyses	Yes	Fair	Methods of allocation concealment NR; no masking reported
Robinson, 2006[162]	Yes	Yes	Yes	Yes	Yes	None, excluded	Yes	Fair	Method of random sequence generation NR; missing data were excluded from analysis
Ruttanaumpa-wan, 2008[184]	Yes	No	No	Yes	Yes	NA?	Yes	Fair	Open-label, randomization and allocation NR, big difference in AHI at BL that would favor CPAP, but they adjusted for it. Good adherence, seems like no attrition.
Siccoli, 2008[164]	Yes	Yes	Yes	Yes	Yes	ITT: LOCF	Yes	Fair	Methods of randomization and allocation concealment NR.

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Smith, 2007[163]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Fair	Unclear methods of allocation concealment; limited reporting of methods for handling missing data (although attrition was not too high, it was 4/26 participants) and likely nothing done to handle missing data
Tomfohr, 2011[186]	Yes	Yes	No	Yes	Yes	None	No, completers analysis	Fair	Methods of randomization and allocation concealment NR; completers only analysis with no handling of missing data, but relatively low attrition and low differential attrition
Toukh, 2012[165]	Yes	No	No	Yes	Yes	1 patient excluded	Partially	Fair	Very small sample size; no masking of patients or providers; methods of allocation concealment NR
Tuomilehto, 2009[211] Tuomilehto, 2010[212] Tuomilehto, 2013[213]	Yes	No	No	NR	Yes	Excluded	Partially	Fair	Open-label, completers only; some analyses adjusted for potential confounders.
Usui, 2005[187]	Yes	No	No	Yes	Yes	NA	Yes	Fair	Very small study; randomization/allocation NR; some differences between groups at BL
Weaver, 2012[166]	Yes	Yes	Yes	Yes for primary outcome and most outcomes; those performing PSGs were not masked	Yes	None (21% of those randomized were not included in analyses in their modified ITT)	No, modified ITT does not include 21% of those randomized	Fair	No handling of missing data; 21% of those randomized not included in analyses

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Weinstock, 2012[167,289]	Yes	Yes	NR	NR	Yes	NR (but just 1 subject with some missing data)	Yes	Fair	Methods of allocation concealment and masking of outcome assessors were not described. Although the sequence 1 group had higher baseline AHI, this is a cross-over and both groups had almost identical AHIs after CPAP and after sham conditions.
West, 2007[168] West, 2009[169]	Yes	Yes	Yes	Yes	Yes	Excluded	Partially	Fair	Missing data excluded; I consider assessors blinded because outcomes of interest were all patient-reported.
Woodson, 2003[203]	Yes for valid and reliable, but seems that timing of assessment differed (although not clear)	Yes	No	Yes	Yes, although specific duration differed by group; not clear how much though	None, excluded	Other than no handling of missing data, acceptable methods	Fair	No handling of missing data; differences in timing/protocol between sham/placebo and the radiofrequency intervention; unclear how much difference in timing of outcome assessments.

Abbreviations: AHEAD=Action for Health in Diabetes; AHI=apnea-hypopnea index; BL=baseline; BOCF=baseline observation carried forward; BP=blood pressure; CPAP=continuous positive airway pressure; CV=cardiovascular; ESS=Epworth Sleepiness Scale; G=group; GEE=generalized estimating equation; HeartBEAT=Heart Biomarker Evaluation in Apnea Treatment; h=hour; HTN=hypertension; IQR=interquartile ratio; ITT=intention to treat; LOCF=last observation carried forward; LAUP=laser assisted uvulopalatoplasty; MAD=mandibular advancement device; MLE=maximum likelihood estimation; MOSAIC=Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular; mth=month; N=number; NA=not applicable; nCPAP=nasal continuous positive airway pressure; NR=not reported; OSA=obstructive sleep apnea; PSG=polysomnography; pts=patients; QOL=quality of life; ROB=risk of bias; RDI=respiratory disturbance index; Sa02=oxygen saturation; SBP=systolic blood pressure; SKUP3=Sleep apnoea Karolinska; TOMADO=trial of oral mandibular advancement devices for obstructive sleep apnoea-hypopnoea; tx=treatment; UPPP=uvulopalatopharygoplasty; VLCD=very low calorie diet; vs.=versus; wks=weeks; yrs=years.

Appendix D Table 8. Quality Ratings of Included Prospective Cohort Studies for KQ 6

First Author, Year	Did the study have differential attrition or overall high attrition raising concern for bias?	Were outcome measurements equal, valid and reliable?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	Did the analysis control for baseline differences between groups?	Does the analysis control for potential confounders? (or are confounders addressed via restriction, matching, or stratification)	Does the analysis account for differences in treatment received by the groups?	Are the statistical methods used to assess the outcomes appropriate?	Quality Rating	Comments
Blackwell, 2015[290] MrOS	No (missing outcome data for 4.5% of the 2,760 who were cognitively intact at baseline and had baseline PSG)	Yes (although unclear whether using the top decile of change for Trails B is a valid way to determine clinically significant decline)	NR	Unknown (mean 3.4 years)	Yes (except perhaps caffeine use)	Yes	Yes, they removed the 197 men using CPAP or oxygen in additional analyses (results were similar)	Yes	Fair	Controlled for a large number of potential cofounders; did not control for caffeine or cholesterol (but controlled for number of comorbid medical conditions); risk of residual confounding; multiple comparisons performed and some findings may be due to chance
Ensrud, 2012[220] MrOS	No (missing vital status for just 1%; 7% of those who were eligible and had PSG at baseline were excluded from analyses, but were known to be living)	Yes	NR	Yes	Unclear (baseline data reported by frailty status, not by AHI categories)	Yes*	Yes, they excluded those who started treatment	Yes	Fair	Controlled for a large number of potential cofounders, but did not control for cardiovascular disease, diabetes, hypertension, cholesterol (but controlled for number of comorbid medical conditions); risk of residual confounding†

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First Author, Year	Did the study have differential attrition or overall high attrition raising concern for bias?	Were outcome measurements equal, valid and reliable?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	Did the analysis control for baseline differences between groups?	Does the analysis control for potential confounders? (or are confounders addressed via restriction, matching, or stratification)	Does the analysis account for differences in treatment received by the groups?	Are the statistical methods used to assess the outcomes appropriate?	Quality Rating	Comments
Gooneratne, 2011[223]	No	Yes	NR‡	Yes	Unclear (baseline data NR by AHI categories; reported by EDS vs. not)	Yes	No	Yes	Fair	
Gottlieb, 2010[224] SHHS	No§	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	Regarding measures, they were valid and reliable measures for CHD; some variation in how they were assessed because it depended on the parent cohort (but it does not seem to differ by AHI, and adjudication methods were similar). For HF, adjudication methods differed across cohorts (but some reassurance from statistical analyses that it didn't matter)

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First Author, Year	Did the study have differential attrition or overall high attrition raising concern for bias?	Were outcome measurements equal, valid and reliable?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	Did the analysis control for baseline differences between groups?	Does the analysis control for potential confounders? (or are confounders addressed via restriction, matching, or stratification)	Does the analysis account for differences in treatment received by the groups?	Are the statistical methods used to assess the outcomes appropriate?	Quality Rating	Comments
Marin, 2005[50]	No	Uncertain; single physician assessed all patients at baseline and during followup	NR (seems unlikely given that a single physician assessed all patients at baseline and during followup)	Yes	Yes	Yes[‖]	Yes	Yes	Fair	
Marshall, 2014[229] Marshall, 2008[228] Busselton Health Study	No	Yes for all-cause mortality; no or uncertain for other outcomes (e.g., no independent adjudication of stroke outcomes; relied on hospital codes)	NR	Yes	Yes	Yes, for all-cause mortality; some limitations for other outcomes (e.g., lacking some cancer risk factors)	No (although they indicate that they think that none were treated)	Yes	Fair for all-cause mortality Poor for other out-comes	Lack of masking outcome assessors of lesser importance when using death index to determine mortality; very wide CIs; lack of precision; only 18 people with moderate to severe OSA; 1 town in Western Australia. High risk of measurement bias and confounding for outcomes other than all-cause mortality

Appendix D Table 8. Quality Ratings of Included Prospective Cohort Studies for KQ 6

First Author, Year	Did the study have differential attrition or overall high attrition raising concern for bias?	Were outcome measurements equal, valid and reliable?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	Did the analysis control for baseline differences between groups?	Does the analysis control for potential confounders? (or are confounders addressed via restriction, matching, or stratification)	Does the analysis account for differences in treatment received by the groups?	Are the statistical methods used to assess the outcomes appropriate?	Quality Rating	Comments
Nieto, 2012[221] WSCS	No	Yes	NR	Yes	Yes	Yes, but small number of events (cancer deaths) yielded imprecise results (7 total cancer deaths in the severe SDB group and 5 in the moderate SDB group)	Yes (included analyses that removed those treated; and the effects increased slightly)	Yes	Fair for cancer mortality	Moderate risk of residual confounding; lack of precise information for Some cancer risk factors (e.g., smoking was current, past, or never, rather than pack-years)
Punjabi, 2009[227] SHHS	No	Yes	Probably[¶]	Yes	Yes	Yes	Yes, excluded those who reported treatment with PAP (n 147)	Yes	Good	
Redline, 2010[225] SHHS	No	Yes	Probably[¶]	Yes	Yes	Yes	Yes, excluded those who reported CPAP use	Yes	Good	
Yaffe, 2011[222]	Yes, overall 35% (163/461 who had PSG were not included in analyses because of death, not completing outcome	Yes	Yes (clinical cognitive status was adjudicated by panel of experts blinded to sleep-disordered breathing	Yes	Yes	Yes[#]	NR	Statistical analyses used appropriate methods, although nothing was done to handle missing data	Fair	Some strengths in controlling for a large number of potential confounders, masked expert panel adjudicating cognitive status, and strength of association increased when

Appendix D Table 8. Quality Ratings of Included Prospective Cohort Studies for KQ 6

First Author, Year	Did the study have differential attrition or overall high attrition raising concern for bias?	Were outcome measurements equal, valid and reliable?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	Did the analysis control for baseline differences between groups?	Does the analysis control for potential confounders? (or are confounders addressed via restriction, matching, or stratification)	Does the analysis account for differences in treatment received by the groups?	Are the statistical methods used to assess the outcomes appropriate?	Quality Rating	Comments
	assessment, or other reasons); differential attrition NR		status)							controlling for baseline cognitive status. Moderate risk of bias due to high attrition (and differential attrition was NR); no handling of missing data; longer followup than 5 years might be needed to better estimate the relationship between OSA and cognitive impairment. Possible applicability limitations
Young, 2008[226] WSCS	No	Yes	NR	Yes	Yes	Yes	Yes (included analyses that removed those treated; and the effect increased)	Yes	Good	

[*] Age, race, site, health status, body mass index, education, social support, alcohol intake, smoking, antidepressant, benzodiazepine, non-benzodiazepine sedative hypnotic use, number of comorbid medical conditions, cognitive function, and baseline frailty status

[†] The ORs they report are 1.74 or 1.88 and just barely reach significance and additional adjustment could alter findings. Possible that the effect could increase over longer followup though (this had shorter followup than some other studies)

[‡] But minimal concern for risk of bias from this with this type of mortality outcome assessment

[§] No followup data or missing covariates for about 10% (476/4422)

[‖] Used matching for age and BMI to select healthy community participants; long list of potential confounders considered in forward stepwise Cox model

[¶] Unclear if masked, but seems likely that some/all/most were given the reliance on the physician review and the parent cohorts that these come from

Appendix D Table 8. Quality Ratings of Included Prospective Cohort Studies for KQ 6

[#] Adjusted for age, race, BMI, education, smoking status, diabetes, hypertension, antidepressant use, benzodiazepine use, and use of non-benzodiazepine anxiolytics; additional models adjusted for baseline cognitive test scores

Abbreviations: AHI=apnea-hypopnea index; CHD=coronary heart disease; EDS=excessive daytime sleepiness; HF=heart failure; HRs=hazard ratios; MrOS=; NR=not reported; OSA=obstructive sleep apnea; PAP=positive airway pressure; PSG=polysomnography; SDB=Sleep Disordered Breathing; SHHS=Sleep Heart Health Study; vs.=versus; WSCS=Wisconsin Sleep Cohort Study.

Appendix D Table 9. Relevance of Systematic Reviews and Meta-Analyses for the Association Between AHI and Health Outcomes (KQ 6)

First Author, Year	Did the review focus on community-based samples (as opposed to sleep clinic populations) or stratify results separately for community-based samples?	Did the review limit to prospective studies?	Did the review focus on studies comparing by different AHI categories/ thresholds, including comparison with people with untreated OSA?	Did the review include relevant health outcomes?	Did the review require that included studies adjust for potential confounders (or use other methods to address potential confounding)?	Is the review directly relevant, providing an adequate answer to our KQ?	Comments
Ge, 2013[91]	No (included 6 studies, and combined community-based and referral populations)	Yes	Yes	Yes (CV and all-cause mortality)	Yes	No	Limited by combining community-based and referral populations; potential spectrum bias in referral populations may lead to overestimate of HR
Kendzerska, 2014[92]	Yes, stratified Tables by population based sample vs. clinical sample	No (also included retrospective studies)	Yes	Yes (death, CV events; also included diabetes and depression)	Yes (required to get in main analysis; if no adjustment they were excluded by quality assessment)	No	Limited by including retrospective and prospective studies; and by approach to synthesis that makes it difficult to pull out the portion(s) relevant for our KQ.
Balk, 2011[1]	No	No (also included retrospective studies)	Yes	Yes (all-cause mortality, CV death, nonfatal CVD, QOL, incident stroke; also included diabetes and hypertension)	Yes	No	Limited by combining community-based and referral populations; potential spectrum bias in referral populations may lead to overestimate of HR; (Inclusion criteria also differ from ours by limiting to studies with at least 500 participants, whereas we did not set a limit)

Abbreviations: CV=cardiovascular; CVD=cardiovascular disease; HR=heart rate; KQ=key question; QOL=quality of life.

Appendix D Table 10. Quality Ratings for Systematic Reviews and Meta-Analyses for the Association Between AHI and Health Outcomes (KQ 6)

First Author, Year	Was the review based on a focused question of interest?	Was the literature search strategy clearly described?	Was there evidence of a substantial effort to search for all relevant research?	Were there explicit inclusion/ exclusion criteria for the selection of studies?	Did at least 2 people independently review studies?	Was the validity of included studies adequately assessed?	Was publication bias assessed?	Was heterogeneity assessed and addressed?	Was the approach used to synthesize the information adequate and appropriate?	Were the authors' conclusions supported by the evidence they presented?	Quality Rating
Ge, 2013[91]	Yes	Yes	Yes	Yes	Yes	Yes, they used 6 items,* but the assessments were not used in data synthesis or interpretation	Yes, but used statistical testing that would not be considered appropriate with so few studies	It was assessed statistically; limited assessment of clinical or methodological heterogeneity	Yes	Yes	Fair
Kendzerska, 2014[92]	Yes	Yes	Yes	Yes	Yes	The method of assessment described is adequate, but some of the individual assessments seem to differ from ours†	No	Yes, through qualitative synthesis	Yes	Yes	Fair
Balk, 2011[1]	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear‡	Yes	Yes	Fair

*Clear inclusion and exclusion criteria; document the loss to followup rate; clear definition of outcome; sufficient duration of followup; control of confounding

†(e.g., adequacy of retrospective studies to account for confounding)

‡Does not mention assessment of heterogeneity related to this part of the report (KQ 4 of their report) in the Methods or Results. From the quality approach used, they give some attention to heterogeneity from risk of bias, but not clear how much they assessed clinical heterogeneity (e.g., differences for community vs. sleep clinic populations) or other methodological heterogeneity

Appendix D Table 11. Quality Ratings of Prospective Cohort Studies Excluded From KQ 6 Due to Poor Quality

First Author, Year	Did the study have differential attrition or overall high attrition raising concern for bias?	Were outcome measurements equal, valid and reliable?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	Did the analysis control for baseline differences between groups?	Does the analysis control for potential confounders? (or are confounders addressed via restriction, matching, or stratification)	Does the analysis account for differences in treatment received by the groups?	Are the statistical methods used to assess the outcomes appropriate?	Quality Rating	Comments
Arzt, 2005[230] WSCS	No	No	NR	Yes	Yes	Yes, but only for age, sex, BMI (limited the number of covariates due to the very small number of events)	No	Yes	Poor	High risk of confounding and moderate risk of measurement bias*
Munoz, 2006[231]	No	No, relying only on hospital records of two local public hospitals† to capture events; otherwise, used appropriate criteria and masked neurologist to review records	Yes (neurologist masked to AHI status)	Yes	Yes	Only adjusted for sex (required significant unadjusted association with stroke to get into multivariate model)‡	Yes (excluded those who started CPAP)	Yes	Poor	High risk of measurement bias and confounding
Saint Martin, 2015[232]	Yes, high overall attrition (only 60% of those with baseline neuropsych evaluation are included in the analysis, 559/929)	See comments	NR	Yes	Yes, for variables they reported baseline data on	Partially, some important potential confounders not evaluated	Yes, those treated with CPAP were excluded from analyses	Yes, but see comments about how they used the measures of cognitive function	Poor	High risk of selection bias, measurement bias, and confounding. High attrition; some important differences between completers and noncompleters; baseline cognitive measures and baseline assessment of AHI were taken at

Appendix D Table 11. Quality Ratings of Prospective Cohort Studies Excluded From KQ 6 Due to Poor Quality

First Author, Year	Did the study have differential attrition or overall high attrition raising concern for bias?	Were outcome measurements equal, valid and reliable?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	Did the analysis control for baseline differences between groups?	Does the analysis control for potential confounders? (or are confounders addressed via restriction, matching, or stratification)	Does the analysis account for differences in treatment received by the groups?	Are the statistical methods used to assess the outcomes appropriate?	Quality Rating	Comments
										different times (2001-2003 vs. 2003-2004); no data on some potential confounders (e.g., medications); outcome analyzed is not in terms of cognitive impairment--although they used measures of cognitive function to construct the outcome, they converted all of the data into cognitive z score changes for the study population

*Outcome measure was self-reported physician diagnosed stroke; small number of events (14 incident strokes) yielded imprecise results; high risk of residual confounding with only adjusting for age, sex, BMI (which may overestimate the effect); and no adjustment or analyses to consider treatment with CPAP (may lead to underestimate of the effect; and this found no statistically significant effect but OR, 3.08)

†They didn't consider running models that force in known risk factors to show us if that would change the result. And this study had relatively small sample size and few events (N=394 participants, and just 20 ischemic stroke events)

‡No information on why this would be adequate capture of events

Abbreviations: CPAP=continuous positive airway pressure; NR=not reported; WSCS=Wisconsin Sleep Cohort Study.

Appendix D Table 12. Quality Ratings for Included Randomized, Controlled Trials That Reported Harms (KQ 8*)

Study, First Author, Year	Were harms pre-specified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Harms Quality Rating	Comments
Aarab, 2011[189]	NR	NR	NR	Yes	Fair	Methods NR, but they reported a lot of harms information
Bäck, 2009[198]	Partially	NR	Partially	Yes	Fair	Harms were prespecified but NR if defined. For pain, the VAS scale doesn't need much explanation. But for drinking, speaking, and opening the mouth (for example), it is less clear what was actually asked or if these are valid, reliable measures.
Bloch, 2000[214]	NR	NR	NR	Yes	Fair	No info on harms assessment, but it looks like they did gather some harms info.
Browaldh, 2013[199] SKUP3	NR	NR	NR	Yes	Fair	No description of methods for harms assessment, but I don't get a sense that there is concern for bias.
Dixon, 2012[200]	NR	NR	Partially	Yes	Fair	Harms are reported in an online appendix table. Authors do not report the timing of events and whether they were during or after the perioperative period.
Durán-Cantolla, 2015[36]	NR	Partially	NR	Yes	Fair	No description of methods for harms assessment
Engleman, 1999[176]	NR	NR	NR	Yes	Fair	No description of methods for harms assessment, but they recorded many.
Ferguson, 2003[201]	NR	NR	NR	Yes	Fair	No info on harms assessment, but it looks like they did gather a lot of harms info.
Hui, 2006[141]	NR	NR	NR	Yes	Fair	Only harm reported was withdrawal due to adverse effects (discomfort)
Johansson, 2009[207]	Yes, prespecified lists of relevant harms; NR if defined	No	Unclear	Yes	Fair	Adverse events from the very low energy diet were noted by the study nurse at each visit (but NR whether they asked about these or if they only reported information raised by subjects), and subsequently classified by

Appendix D Table 12. Quality Ratings for Included Randomized, Controlled Trials That Reported Harms (KQ 8*)

Study, First Author, Year	Were harms pre-specified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Harms Quality Rating	Comments
						the study physician for potential causality (unclear how this was determined)
Johnston, 2002[195]	Yes	Partially	NR	Yes	Fair	
Kushida, 2012[145]	NR	NR	Yes (equal); NR for valid and reliable	Yes	Fair	
Lam, 2007[180]	NR	Partially	NR	Yes	Fair	"Side effects of treatment were evaluated by self-reporting using questionnaires in a clinical setting." Implied pre-specification and definition.
Malow, 2008[150]	NR	Partially	NR	Yes	Fair	
Naismith, 2005[192] Gotsopoulos, 2002[193] Gotsopoulos, 2004[194]	Partially	Yes	Unclear	Yes	Fair	"A self-administered detailed, in-house questionnaire was used to document…treatment-related side effects…"
Petri, 2008[191]	NR	NR	NR	Yes	Fair	No description of methods for harms assessment. However, The harms they are reporting were discontinuation due to adverse effects, and the reasons for discontinuation. Therefore, not much concern for high risk of bias despite limited reporting.
Quinnell, 2014[197]	NR	NR	NR	Yes	Fair	No description of methods for harms assessment. However, The harms they are reporting were discontinuation due to adverse effects, and the reasons for discontinuation; therefore, not high risk of bias despite limited reporting.
Redline, 1998[183]	NR	NR	NR	Yes	Fair	No info on harms assessment, but it looks like they did gather a lot of harms info based on the Results reported.

Appendix D Table 12. Quality Ratings for Included Randomized, Controlled Trials That Reported Harms (KQ 8*)

Study, First Author, Year	Were harms pre-specified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Harms Quality Rating	Comments
Smith, 2007[163]	NR	NR	NR	Yes	Fair	No info on harms assessment, but it looks like they did gather a lot of harms info based on the Results reported.
Weaver, 2012[166]	NR	NR	NR	Yes	Fair	Methods NR, but they reported a lot of harms information
Woodson, 2003[203]	Yes	Yes	Yes	Yes	Fair	

*The quality rating assessments for these studies that re in the tables above for KQ 4 and 5 also contribute information toward the overall quality ratings for harms

Abbreviations: NR=not reported; SKUP3=Sleep apnoea Karolinska uvulopalatopharyngoplasty; VAS=visual analog scale.

Appendix E Table 1. Characteristics of Included Studies of Type II Portable Monitors for KQ 3

First Author, Year Country	PM Name PM Type (Number of Channels) PM Channels*	PM Setting PM Timing	N Enrolled (N Analyzed)	Mean (SD) AHI [Range]	Mean (SD) ESS [Range]	Mean Age, Yr	% Female	Mean BMI, kg/m^2	Participants	% With OSA According to Specific PSG AHI Cutpoints	Quality
Bruyneel, 2011[110] Belgium	Pamela V 3.631 II (10) 1–5, 7–11	Home Different time	66 (62)	26 (30) [NR]	10 (5.0) [NR]	49	41	30	Consecutive patients referred to sleep lab for clinical suspicion of OSA	AHI ≥5: 81 AHI ≥15: 44 AHI ≥30: 31	Fair
Campbell, 2011[111] New Zealand	Siesta Sleep System II (11) 1–5, 7–12	Home Different time	31 (30)	35 (29) [NR]	11 (4.9) [0–20]	49	20	31	Consecutive patients referred for possible OSA without significant comorbidity	AHI >10: 70	Fair
Ferré, 2012[109] Spain	Somté II (11) 1–3, 6–11	Sleep lab Simultaneous	NR (68)	Scorer 1: 22 (10) [NR] Scorer 2: 20 (18.8) [NR]	9 (9.5) [15–81]	56	43	29	Patients with suspected sleep apnea referred to sleep unit	AHI ≥5: 81 AHI ≥15: 53 AHI ≥30: 26	Good

* 1=oxygen saturation from pulse oximetry; 2=electroencephalogram; 3=electro-oculogram; 4=electromyogram; 5=electrocardiogram; 6=heart rate; 7=snoring; 8=airflow; 9=chest wall motion; 10=abdomen motion; 11=body position; 12=leg movements; 13=thermal flow; 14=photoplethlysmograph; 15=peripheral arterial tone; 16=wrist activity

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; ESS=Epworth Sleepiness Scale; kg=kilograms; m=meters; N=sample size; NR=not reported; OSA=obstructive sleep apnea; PM=portable monitor; PSG=polysomnography; SD=standard deviation; yr=years.

Appendix E Table 2. Characteristics of Included Studies of Type III Portable Monitors for KQ3

First Author, Year Country	PM Name PM Type (Number of Channels) PM Channels*	PM Setting PM Timing	N Enrolled (N Analyzed)	Mean (SD) AHI [Range]	Mean (SD) ESS [Range]	Mean Age, Yr	% Female	Mean BMI, kg/m^2	Participants	% With OSA According to Specific PSG AHI Cutpoints	Quality
Guerrero, 2014[113] Spain	3N-PM III (5) 1, 8–10, 13	Home Different time	56 (56)	30 (22.4) [NR]	10 (5.3) [NR]	54	45	30	Patients referred to sleep unit with mild-moderate clinical suspicion of OSA or with significant comorbidity that induced frequent symptoms mimicking those of OSA	AHI >5: 95	Good
Pereira, 2013[114] Canada	MediByte III (5) 1, 8–11	Home Different time	128 (128)	Berlin Low: 25 (29.7) [NR] High: 35 (27.0) [NR] SACS Low: 19 (15.6) [NR] Intermediate: 39 (27.5) [NR] High: 39 (31.3) [NR] STOP-Bang Low: 15 (13.7) [NR] High: 36 (28.0) [NR]	NR	50	34	31	Patients referred to sleep clinic	AHI >5: 91	Good

*1=oxygen saturation from pulse oximetry; 2=electroencephalogram; 3=electro-oculogram; 4=electromyogram; 5=electrocardiogram; 6=heart rate; 7=snoring; 8=airflow; 9=chest wall motion; 10=abdomen motion; 11=body position; 12=leg movements; 13=thermal flow; 14=photoplethlysmograph; 15=peripheral arterial tone; 16=wrist activity

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; ESS=Epworth Sleepiness Scale; kg=kilograms; m=meters; N=sample size; OSA=obstructive sleep apnea; PM=portable monitor; PSG=polysomnography; SACS=Sleep Apnea Clinical Score; SD=standard deviation; yr=years.

Appendix E Table 3. Characteristics of Included Studies of Type IV (3+ Channels) Portable Monitors for KQ3

First Author, Year Country	PM Name PM Type (Number of Channels) PM Channels*	PM Setting PM Timing	N Enrolled (N Analyzed)	Mean (SD) AHI [Range]	Mean (SD) ESS [Range]	Mean Age, Yr	% Female	Mean BMI, kg/m^2	Participants	% With OSA According to Specific PSG AHI Cutpoints	Quality
Barak-Shinar, 2013[115] Israel	Morpheus Ox IV (3) 1, 6, 14	Sleep lab Simultaneous	140 (140)	16 (17.4) [NR]	10.2 (NR) [NR]	53	44	31	Patients referred to sleep lab due to suspected risk of OSA	AHI ≥5: 72 AHI ≥15: 39	Fair
Choi, 2010[125] Korea	Watch-PAT 100 IV (4) 1, 6, 15, 16	Hospital Different time	27 (25)	32 (28.9) [NR]	NR	41	16	26	Adult subjects with suspected OSA	AHI ≥5: 76 AHI ≥15: 68 AHI ≥30: 44	Fair
Garg, 2014[127] United States	Watch-PAT 200 IV (6) 1, 6, 7, 11, 12, 15	Home and sleep lab Simultaneous and different time	75 (75)	30 (35.0) [NR]	12 (5.5) [NR]	45	76	NR	Patients recruited from primary care and sleep clinics who were considered to be high risk for OSA as determined by Berlin questionnaire	AHI >5: 71	Good
Gurubhagavatula, 2013[104] United States	AutoSet IV (4) 1†, 8, 9, 10	Home Different time	250 (250)‡	23 (22.9) [NR]	NR	53	20	32	Outpatients with hypertension recruited from internal medical practices at the VA and a university hypertension clinic	Any OSA (AHI ≥5): 80 Mild OSA (AHI=5-14.9): 34 Moderate OSA (AHI=15-29.9): 22 Severe OSA (AHI ≥30): 25 Any OSAS (AHI ≥5 and	Fair

Appendix E Table 3. Characteristics of Included Studies of Type IV (3+ Channels) Portable Monitors for KQ3

First Author, Year Country	PM Name PM Type (Number of Channels) PM Channels*	PM Setting PM Timing	N Enrolled (N Analyzed)	Mean (SD) AHI [Range]	Mean (SD) ESS [Range]	Mean Age, Yr	% Female	Mean BMI, kg/m^2	Participants	% With OSA According to Specific PSG AHI Cutpoints	Quality
										ESS>10): 25 s-OSAS (AHI ≥30 and ESS>10): 8	
Masa, 2011[119]; Masa, 2013[291] Spain	BreastSC20 IV (5) 1, 8–11	Home Different time	366 (348)	38 (NR) [NR]	12 (5.0) [NR]	49	24	31	Patients referred for pulmonary consultation due to suspected OSA (snoring, observed apneas, ESS>10, or non-refreshing sleep)	AHI ≥5: 80 AHI ≥15: 22	Good

* 1=oxygen saturation from pulse oximetry; 2=EEG; 3=electro-oculogram; 4=electromyogram; 5=electrocardiogram; 6=heart rate; 7=snoring; 8=airflow; 9=chest wall motion; 10=abdomen motion; 11=body position; 12=leg movements; 13=thermal flow; 14=photoplethlysmograph; 15=peripheral arterial tone; 16=wrist activity

† Oximetry was worn according to manufacturer's directions but was not used in automated scoring because desaturation was not required to score apneas or hypopneas.

ǂ Of the 250 participants, 242 completed the ESS, 198 completed a PSG, and 192 completed a PM evaluation; missing data were imputed prior to analysis.

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; ESS=Epworth Sleepiness Scale; kg=kilograms; m=meters; N=sample size; OSA=obstructive sleep apnea; PM=portable monitor; PSG=polysomnography; SD=standard deviation; yr=years.

Appendix E Table 4. Characteristics of Included Studies of Type IV (2 Channels) Portable Monitors for KQ3

First Author, Year Country	PM Name PM Type (Number of Channels) PM Channels*	PM Setting PM Timing	N Enrolled (N Analyzed)	Mean (SD) AHI [Range]	Mean (SD) ESS [Range]	Mean Age, Yr	% Female	Mean BMI, kg/m^2	Participants	% With OSA According to Specific PSG AHI Cutpoints	Quality
Alvarez, 2009[126] Spain	Criticare 504 Pulse Oximeter IV (2) 1, 6	Sleep lab Simultaneous	187 (187)	AHI ≥10: 40 (19.6) [NR] AHI<10: 2.0 (2.4) [NR]	NR	58	21	30	Patients with suspected OSA	AHI >10: 59	Good
Nigro, 2010[124] Argentina	ApneaLink IV (2)† 7, 8	Sleep lab Simultaneous	76 (66)	10 (NR) [4.1- 34.1]	NR	52	29	29	Consecutive patients referred for possible sleep apnea hypopnea syndrome	Mild (RDI=5-<15): 30 Moderate (RDI=15-<30): 21 Severe (RDI ≥30): 26	Fair
Nigro, 2013[117] Argentina	ApneaLink Ox IV (2) 1, 8	Sleep lab Simultaneous	55 (55)	NR‡	NR	48	31	30	Patients with suspected OSA referred to clinic	RDI ≥5: 78	Good
Poupard, 2012[120] France	Nonin WristOx IV (2) 1, 6	Sleep lab Simultaneous	106 (106)	NR	NR AHI<5: 11 (7) [NR]; 5≤AHI<15: 8 (5) [NR]; 15≤AHI<30: 9 (5) [NR]; AHI ≥30: 10 (6) [NR]	57	35	29	Consecutive patients referred to sleep laboratory for suspected sleep apnea syndrome	AHI ≥15: 50	Fair

Appendix E Table 4. Characteristics of Included Studies of Type IV (2 Channels) Portable Monitors for KQ3

First Author, Year Country	PM Name PM Type (Number of Channels) PM Channels*	PM Setting PM Timing	N Enrolled (N Analyzed)	Mean (SD) AHI [Range]	Mean (SD) ESS [Range]	Mean Age, Yr	% Female	Mean BMI, kg/m^2	Participants	% With OSA According to Specific PSG AHI Cutpoints	Quality
Yadollahi, 2010[123] Canada	Acoustical Sleep Apnea Diagnosis (ASAD) System§ IV (2) 1, 7	Sleep lab Simultaneous	66 (66)	24 (30.3) [0.2-125.7]	NR	51	27	32	Population already undergoing full-night PSG study	AHI ≥5: NR	Fair

* 1=oxygen saturation from pulse oximetry; 2=EEG; 3=electro-oculogram; 4=electromyogram; 5=electrocardiogram; 6=heart rate; 7=snoring; 8=airflow; 9=chest wall motion; 10=abdomen motion; 11=body position; 12=leg movements; 13=thermal flow; 14=photoplethlysmograph; 15=peripheral arterial tone; 16=wrist activity

† Authors describe ApneaLink as a single-channel portable monitor that measures airflow; we reclassified it as a dual-channel portable monitor since it also measures snoring.

ǂ The mean RDI was 15 (NR) [6-35].

§ The ASAD system included an omnidirectional microphone (Sony ECM-77B) and Masimo pulse oximeter.

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; ESS=Epworth Sleepiness Scale; kg=kilograms; m=meters; N=sample size; OSA=obstructive sleep apnea; PM=portable monitor; PSG=polysomnography; RDI=respiratory disturbance index; SD=standard deviation; yr=years.

Appendix E Table 5. Characteristics of Included Studies of Type IV (1 Channel) Portable Monitors for KQ3

First Author, Year Country	PM Name PM Type (Number of Channels) PM Channel	PM Setting PM Timing	N Enrolled (N Analyzed)	Mean (SD) AHI [Range]	Mean (SD) ESS [Range]	Mean Age, yr	% Female	Mean BMI, kg/m^2	Participants	% With OSA According to Specific PSG AHI Cutpoints	Quality
Alvarez, 2012[118] Spain	Nonin PureSAT IV (1) Oxygen saturation from pulse oximetry	Sleep lab Simultaneous	240 (240)*	OSA-positive patients: 37 (25.7) [NR] OSA-negative patients: 4 (2.4) [NR]	NR	52	24	30	Subjects who showed high suspicion of suffering from OSA based on clinical evaluation and referred to a hospital's sleep unit	AHI ≥10: 67	Fair
Bohning, 2011[121] Germany	WristOx 3100 IV (1) Oxygen saturation from pulse oximetry	Sleep lab Simultaneous	135 (135)	NR	NR	55	18	32	Patients who had undergone a prior cardiorespiratory polygraphy exam and were referred to the sleep lab	AHI ≥5: 87	Fair
Morillo, 2013[116] Spain	70750A19 (Jaeger) Pulse Oximeter IV (1) Oxygen saturation from pulse oximetry	Sleep lab Simultaneous	115 (115)	23 (25.1) [NR]	NR	61	17	32	Referred to the sleep unit of the University Hospital with suspected SAHS	AHI ≥10: 57	Fair
Rofail, 2010[122] Australia	FlowWizard IV (1)† Airflow RadicalSet IV (1)† Oxygen saturation from pulse oximetry	Home Different time	98 (92)	19 (21.2) [NR]	10 (5.0) [NR]	46	23	30	Referred to the Sleep Disorders Clinic for evaluation of possible OSA	AHI ≥5: 71 AHI ≥30: 25	Fair

* The overall study sample was distributed among a training set (n=96) and a test set (n=144).
† Authors evaluated two single-channel portable monitors, separately.

Appendix E Table 5. Characteristics of Included Studies of Type IV (1 Channel) Portable Monitors for KQ3

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; ESS=Epworth Sleepiness Scale; kg=kilograms; m=meters; N=sample size; OSA=obstructive sleep apnea; PM=portable monitor; PSG=polysomnography; SD=standard deviation; yr=years.

Appendix E Table 6. Results of Newly Identified, Included Studies for KQ 3: Accuracy of Diagnostic Tests (Type II Portable Monitors)

First Author, Year	PM Name PM Setting	PSG AHI Cutpoint PM AHI Cutpoint	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Pos LR (95% CI)	Neg LR (95% CI)
Bruyneel, 2011[110]	Pamela V 3.631 Home	AHI ≥5 NR	96.0 (NR)	71.0 (NR)	NR	NR	NR
Bruyneel, 2011[110]	Pamela V 3.631 Home	AHI ≥20 NR	76.0 (NR)	85.0 (NR)	NR	NR	NR
Bruyneel, 2011[110]	Pamela V 3.631 Home	AHI ≥30 NR	86.0 (NR)	100.0 (NR)	NR	NR	NR
Campbell, 2011[111]	Siesta Sleep System Home	AHI >5 NR	88.0 (NR)	50.0 (NR)	0.900 (NR)	1.76 (NR)	0.24 (NR)
Campbell, 2011[111]	Siesta Sleep System Home	AHI >10 NR	90.5 (NR)	88.9 (NR)	0.921 (NR)	8.14 (NR)	0.11 (NR)
Campbell, 2011[111]	Siesta Sleep System Home	AHI >15 NR	93.7 (NR)	76.9 (NR)	0.942 (NR)	4.06 (NR)	0.08 (NR)
Ferré, 2012[109]	Somté Lab	AHI ≥5 NR	Scorer 1: 91.0 (NR) Scorer 2: 90.0 (NR) Average: 90.5	Scorer 1: 77.0 (NR) Scorer 2: 90.0 (NR) Average: 83.5	Scorer 1: 0.810 (0.660, 0.960) Scorer 2: 0.900 (0.780, 1.000) Average: 85.5	Scorer 1: 4.00 (NR) Scorer 2: 9.00 (NR) Average: 6.5	Scorer 1: 0.12 (NR) Scorer 2: 0.11 (NR) Average: 0.12
Ferré, 2012[109]	Somté Lab	AHI ≥15 NR	Scorer 1: 86.0 (NR) Scorer 2: 83.0 (NR) Average: 84.5	Scorer 1: 97.0 (NR) Scorer 2: 92.0 (NR) Average: 94.5	Scorer 1: 0.900 (0.820, 0.980) Scorer 2: 0.880 (0.780, 0.970) Average: 0.89	Scorer 1: 24.70 (NR) Scorer 2: 10.50 (NR) Average: 17.6	Scorer 1: 0.14 (NR) Scorer 2: 0.18 (NR) Average: 0.16
Ferré, 2012[109]	Somté Lab	AHI ≥30 NR	Scorer 1: 61.0 (NR) Scorer 2: 67.0 (NR) Average: 64.0	Scorer 1: 96.0 (NR) Scorer 2: 100.0 (NR) Average: 98.0	Scorer 1: 0.860 (0.730, 0.990) Scorer 2: 0.830 (0.700, 0.97) Average: 84.5	Scorer 1: 15.30 (NR) Scorer 2: 2.00 (NR) Average: 8.65	Scorer 1: 0.41 (NR) Scorer 2: 0.33 (NR) Average: 0.37

Abbreviations: AHI=apnea-hypopnea index; AUROC=area under receiver operating characteristic curve; LR=likelihood ratio; Neg=negative; NR=not reported; PM=portable monitor; Pos=positive; PSG=polysomnography.

Appendix E Table 7. Results of Newly Identified, Included Studies for KQ 3: Accuracy of Diagnostic Tests (Type III Portable Monitors)

First Author, Year	PM Name PM Setting	PSG AHI Cutpoint PM AHI Cutpoint	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Pos LR (95% CI)	Neg LR (95% CI)
Guerrero, 2014 [*113]	3N-PM Home	AHI ≥5 AHI ≥5[†]	96.2 (NR)	66.7 (NR)	0.955 (0.862, 0.993)	2.88 (0.60 14.30)	0.06 (0.01, 0.30)
Guerrero, 2014 [*113]	3N-PM Home	AHI ≥10 NR	NR	NR	0.942 (0.844, 0.987)	NR	NR
Guerrero, 2014 [*113]	3N-PM Home	AHI ≥15 AHI<7[‡]	94.9 (NR)	56.2 (NR)	0.852 (0.730, 0.933)	2.17 (1.20, 3.80)	0.09 (0.02, 0.40)
Guerrero, 2014 [*113]	3N-PM Home	AHI ≥15 AHI ≥22[‡]	48.7 (NR)	93.7 (NR)	0.852 (0.730, 0.933)	7.79 (1.10, 53.40)	0.55 (0.40, 0.80)
Guerrero, 2014 [*113]	3N-PM Home	AHI ≥30 NR	NR	NR	0.900 (0.789, 0.965)	NR	NR
Pereira, 2013[114]	MediByte Home	AHI ≥5 NR	87.0 (NR)	67.0 (NR)	NR	2.60 (NR)	0.20 (NR)
Pereira, 2013[114]	MediByte Home	AHI ≥10 NR	79.0 (NR)	86.0 (NR)	0.824 (NR)	5.50 (NR)	0.20 (NR)
Pereira, 2013[114]	MediByte Home	AHI ≥15 NR	77.0 (NR)	95.0 (NR)	NR	15.50 (NR)	0.20 (NR)
Pereira, 2013[114]	MediByte Home	AHI ≥30 NR	50.0 (NR)	93.0 (NR)	NR	7.20 (NR)	0.50 (NR)

[*] Authors obtained the mean values for 3 nights of PM use and compared them to PSG.
[†] For a PSG≥5, authors report that a PM AHI<5 would exclude and a PM AHI ≥5 would confirm OSA diagnosis.
[‡] For a PSG≥15, authors report that a PM AHI<7 would exclude and a PM AHI ≥22 would confirm OSA diagnosis.

Abbreviations: AHI=apnea-hypopnea index; AUROC=area under receiver operating characteristic curve; LR=likelihood ratio; Neg=negative; NR=not reported; PM=portable monitor; Pos=positive; PSG=polysomnography.

Appendix E Table 8. Results of Newly Identified, Included Studies for KQ 3: Accuracy of Diagnostic Tests (Type IV Portable Monitors With 3+ Channels)

First Author, Year	PM Name PM Setting	PSG AHI Cutpoint PM AHI Cutpoint	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Pos LR (95% CI)	Neg LR (95% CI)
Barak-Shinar, 2013[115]	Morpheus Ox Lab	AHI ≥5 AHI ≥5	97.0 (91.6, 99.4)	97.4 (86.5, 99.9)	NR	NR	NR
Barak-Shinar, 2013[115]	Morpheus Ox Lab	AHI ≥15 AHI ≥15	94.4 (84.6, 98.8)	96.5 (90.1, 99.3)	NR	NR	NR
Choi, 2010[125]	Watch-PAT 100 Home	AHI ≥5 NR	100.0 (NR)	83.0 (NR)	NR	NR	NR
Choi, 2010[125]	Watch-PAT 100 Home	AHI ≥15 NR	81.0 (NR)	77.0 (NR)	NR	NR	NR
Choi, 2010[125]	Watch-PAT 100 Home	AHI ≥30 NR	92.0 (NR)	92.0 (NR)	NR	NR	NR
Garg, 2014[127]	Watch-PAT 200 Lab, Home	AHI ≥5 NR	Lab: NR Home: 96.0 (85.0, 99.0)	Lab: NR Home: 43.0 (22.0, 66.0)	Lab: 0.940 (NR) Home: 0.909 (NR)	Lab: 1.70 (NR) Home: 1.67 (1.15, 2.44)	Lab: NR Home: 0.01 (0.02, 0.42)
Garg, 2014[127]	Watch-PAT 200 Lab, Home	AHI ≥10 NR	Lab: NR Home: 90.0 (77.0, 97.0)	Lab: NR Home: 69.0 (48.0, 86.0)	Lab: 0.960 (NR) Home: 0.946 (NR)	Lab: NR Home: 2.94 (1.64, 5.28)	Lab: NR Home: 0.14 (0.05, 0.36)
Garg, 2014[127]	Watch-PAT 200 Lab, Home	AHI ≥15 NR	Lab: NR Home: 92.0 (79.0, 98.0)	Lab: NR Home: 77.0 (58.0, 90.0)	Lab: 0.960 (NR) Home: 0.922 (NR)	Lab: NR Home: 3.95 (2.05, 7.60)	Lab: NR Home: 0.10 (0.03, 0.31)
Gurubhagavatula, 2013[104]	AutoSet PDS Home	AHI ≥5[*] AHI cutpoint=8.9	71.8 (NR)	47.8 (NR)	0.591 (NR)	NR	0.57 (NR)
Gurubhagavatula, 2013[104]	AutoSet PDS Home	AHI ≥30[†] AHI cutpoint=16	74.7 (NR)	70.6 (NR)	0.727 (NR)	NR	0.36 (NR)
Masa, 2011[119]	BreastSC20 Home	AHI ≥5 Multiple[‡]	PM AHI ≥5: 96.0 (NR) PM AHI ≥10: 87.0 (NR)	PM AHI ≥5: 57.0 (NR) PM AHI ≥10: 86.0 (NR)	0.917 (0.864, 0.969)	PM AHI ≥5: 2.23 (1.78, 2.79) PM AHI ≥10: 6.25 (2.73, 14.00)	PM AHI ≥5: 0.07 (0.05, 0.10) PM AHI ≥10: 0.15 (0.11, 0.21)

Appendix E Table 8. Results of Newly Identified, Included Studies for KQ 3: Accuracy of Diagnostic Tests (Type IV Portable Monitors With 3+ Channels)

First Author, Year	PM Name PM Setting	PSG AHI Cutpoint PM AHI Cutpoint	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Pos LR (95% CI)	Neg LR (95% CI)
Masa, 2011[119]	BreastSC20 Home	AHI ≥10 Multiple‡	PM AHI ≥5: 97.0 (NR) PM AHI ≥20: 71.0 (NR)	PM AHI ≥5: 39.0 (NR) PM AHI ≥20: 90.0 (NR)	0.883 (0.845, 0.933)	PM AHI ≥5: 1.59 (1.30, 1.94) PM AHI ≥20: 7.10 (3.37, 15.00)	PM AHI ≥5: 0.08 (0.04, 0.16) PM AHI ≥20: 0.32 (0.26, 0.39)
Masa, 2011[119]	BreastSC20 Home	AHI ≥15 Multiple‡	PM AHI ≥10: 94.0 (NR) PM AHI ≥25: 67.0 (NR)	PM AHI ≥10: 60.0 (NR) PM AHI ≥25: 92.0 (NR)	0.891 (0.859, 0.933)	PM AHI ≥10:2.35 (1.81, 3.05) PM AHI ≥25: 8.36 (4.09, 17.00)	PM AHI ≥10: 0.10 (0.06, 0.17) PM AHI ≥25: 0.36 (0.30, 0.44)

* Authors defined any obstructive sleep apnea syndrome as AHI ≥5 and Epworth Sleepiness Scale >10.
ǂ Authors defined severe obstructive sleep apnea syndrome as AHI ≥30 and Epworth Sleepiness Scale >10.
‡ Authors reported exclusionary and confirmatory PM AHI cutpoints for each level of the PSG AHI.

Abbreviations: AHI=apnea-hypopnea index; AUROC=area under receiver operating characteristic curve; LR=likelihood ratio; Neg=negative; NR=not reported; PM=portable monitor; Pos=positive; PSG=polysomnography.

Appendix E Table 9. Results of Newly Identified, Included Studies for KQ 3: Accuracy of Diagnostic Tests (Type IV Portable Monitors With 2 Channels)

First Author, Year	PM Name PM Setting	PSG AHI Cutpoint PM AHI Cutpoint	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Pos LR (95% CI)	Neg LR (95% CI)
Alvarez, 2009[126]	Criticare 504 Lab	AHI ≥10 NR	Classical MSC*: 69.2 (NR) Cross-ApEn*: 83.7 (NR)	Classical MSC*: 90.9 (NR) Cross-ApEn*: 84.3 (NR)	Classical MSC*: 0.781 (NR) Cross-ApEn*: 0.840 (NR)	NR	NR
Nigro, 2010[124]	ApneaLink Lab	RDI ≥5 Multiple	PM RI>9: 80.4 (66.9, 91.4) PM AHI ≥5: 88.2 (76.1, 95.5)	PM RI>9: 100.0 (78.0, 100.0) PM AHI ≥5: 86.7 (59.5, 98.0)	PM RI>9: 0.900 (0.800, 0.960) PM AHI ≥5: 0.875 (0.770, 0.940)	PM RI>9:NR PM AHI ≥5: 6.60 (5.30, 8.30)	PM RI>9: 0.20 (NR) PM AHI ≥5: 0.14 (0.03, 0.60)
Nigro, 2010[124]	ApneaLink Lab	RDI ≥10 Multiple	PM RI>13: 91.7 (77.5, 98.2) PM AHI ≥10: 88.9 (73.9, 96.8)	PM RI>13: 93.3 (77.9, 99.0) PM AHI ≥10: 90.0 (73.4, 97.8)	PM RI>13: 0.920 (0.830, 0.970) PM AHI ≥10: 0.890 (0.790, 0.960)	PM RI>13: 13.70 (12.00, 15.80) PM AHI ≥10: 8.90 (7.50, 10.50)	PM RI>13: 0.09 (0.02, 0.50) PM AHI ≥10: 0.12 (0.03, 0.50)
Nigro, 2010[124]	ApneaLink Lab	RDI ≥15 Multiple	PM RI>16: 93.5 (78.5, 99.0) PM AHI ≥15: 93.5 (78.5, 99.0)	PM RI>16: 91.4 (76.9, 98.1) PM AHI ≥15: 91.4 (76.9, 98.1)	PM RI>16: 0.950 (0.870, 0.990) PM AHI ≥15: 0.925 (0.830, 0.975)	PM RI>16: 10.9 (9.50, 12.50) PM AHI ≥15: 10.9 (9.50, 12.50)	PM RI>16: 0.07 (0.01, 0.40) PM AHI ≥15: 0.07 (0.01, 0.40)
Nigro, 2010[124]	ApneaLink Lab	RDI ≥30 AHI ≥30	100.0 (80.5, 100.00)	89.8 (77.8, 96.6)	NR	9.80 (8.90, 10.80)	0.00 (NR)
Nigro, 2013[117]	ApneaLink Ox (Automatic Scoring)† Lab	RDI ≥5 AHI ≥5	O_2 saturation≥3%: 90.7 (77.9, 97.4) O_2 saturation≥4%: 76.7 (61.4, 88.2)	O_2 saturation≥3%: 83.3 (51.6, 97.9) O_2 saturation≥4%: 91.7 (61.5, 99.8)	O_2 saturation≥3%: 0.870 (NR) O_2 saturation≥4%: 0.840 (NR)	O_2 saturation≥3%: 5.40 (NR) O_2 saturation≥4%: 9.20 (NR)	O_2 saturation≥3%: 0.11 (NR) O_2 saturation≥4%: 0.25 (NR)
Nigro, 2013[117]	ApneaLink Ox (Manual Scoring) Lab	RDI ≥5 AHI ≥5	93.0 (80.9, 98.5)	91.7 (61.5, 99.8)	0.923 (NR)	11.60 (NR)	0.08 (NR)
Poupard, 2012[120]	Nonin WristOx Lab	AHI >5 NR	65.0 (NR)	100.0 (NR)	NR	NR	NR
Poupard, 2012[120]	Nonin WristOx Lab	AHI >15 NR	58.0 (NR)	100.0 (NR)	NR	NR	NR
Poupard, 2012[120]	Nonin WristOx Lab	AHI >30 NR	59.0 (NR)	100.0 (NR)	NR	NR	NR

Appendix E Table 9. Results of Newly Identified, Included Studies for KQ 3: Accuracy of Diagnostic Tests (Type IV Portable Monitors With 2 Channels)

First Author, Year	PM Name PM Setting	PSG AHI Cutpoint PM AHI Cutpoint	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Pos LR (95% CI)	Neg LR (95% CI)
Yadollahi, 2010[123]	ASAD‡ Lab	AHI ≥5 AHI ≥8.6	74.3 (NR)	82.4 (NR)	0.870 (NR)	NR	NR
Yadollahi, 2010[123]	ASAD‡ Lab	AHI ≥10 AHI ≥13	82.8 (NR)	91.1 (NR)	0.950 (NR)	NR	NR
Yadollahi, 2010[123]	ASAD‡ Lab	AHI ≥15 AHI ≥18.5	84.6 (NR)	96.0 (NR)	0.960 (NR)	NR	NR
Yadollahi, 2010[123]	ASAD‡ Lab	AHI ≥20 AHI ≥23	91.6 (NR)	97.8 (NR)	0.990 (NR)	NR	NR

* Oximetry signals were processed by means of a classical frequency analysis based on the magnitude squared coherence (Classical MSC) and a nonlinear analysis based on the means of cross-approximate entropy, a recently developed measure of synchrony (Cross-ApEn).
ⁱ A hypopnea was defined in two different ways: decrease in airflow≥30% of baseline for at least 10 seconds plus oxygen desaturation (1) ≥3% or (2) ≥4%.
‡ The acoustical sleep apnea diagnosis (ASAD) system included an omnidirectional microphone (Sony ECM-77B) and Masimo pulse oximeter.

Abbreviations: AHI=apnea-hypopnea index; ASAD=acoustical sleep apnea diagnosis; AUROC=area under receiver operating characteristic curve; Cross-ApEn=cross-approximate entropy; LR=likelihood ratio; MSC=magnitude squared coherence; Neg=negative; NR=not reported; PM=portable monitor; Pos=positive; PSG=polysomnography; RDI=respiratory disturbance index; RI=risk indicator.

Appendix E Table 10. Results of Newly Identified, Included Studies for KQ 3: Accuracy of Diagnostic Tests (Type IV Portable Monitors With 1 Channel)

First Author, Year	PM Name PM Setting	PSG AHI Cutpoint PM AHI Cutpoint	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Pos LR (95% CI)	Neg LR (95% CI)
Alvarez, 2012[118]	Nonin PureSAT Lab	AHI ≥10 NR	89.1 (NR)	87.5 (NR)	NR	NR	NR
Bohning, 2011[121]	WristOX 3100 Lab	AHI ≥5 NR	100.0 (NR)	35.0 (NR)	NR	NR	NR
Morillo, 2013[116]	70750A19 (Jaeger) pulse oximeter Sleep lab	AHI ≥10 NR	$ODI4_{40}$: 86.4 (NR) $ODI4_{30}$: 84.9 (NR) $ODI3_{40}$: 81.8 (NR) $ODI3_{30}$: 84.9 (NR)	$ODI4_{40}$: 89.8 (NR) $ODI4_{30}$: 93.4 (NR) $ODI3_{40}$: 77.6 (NR) $ODI3_{30}$: 75.5 (NR)	$ODI4_{40}$: 0.903 (NR) $ODI4_{30}$: 0.890 (NR) $ODI3_{40}$: 0.860 (NR) $ODI3_{30}$: 0.835 (NR)	$ODI4_{40}$: 8.5 $ODI4_{30}$: 13.9 $ODI3_{40}$: 3.6 $ODI3_{30}$: 3.5	$ODI4_{40}$: 0.15 $ODI4_{30}$: 0.16 $ODI3_{40}$: 0.23 $ODI3_{30}$: 0.2
Rofail, 2010[122]	Flow Wizard Home	AHI ≥5 NR	Single Night: 75.0 (63.0, 85.0) Averaged Over Multiple Nights: 80.0 (67.0, 93.0)	Single Night: 79.0 (61.0, 97.0) Averaged Over Multiple Nights: 87.0 (77.0, 97.0)	Single Night: 0.800 (0.700, 0.910) Averaged Over Multiple Nights: 0.850 (0.760, 0.910)	Single Night: 3.60 (NR) Averaged Over Multiple Nights: 6.30 (NR)	Single Night: 0.30 (NR) Averaged Over Multiple Nights: 0.23 (NR)
Rofail, 2010[122]	Flow Wizard Home	AHI ≥30 NR	Single Night: 90.0 (84.0, 98.0) Averaged Over Multiple Nights: 90.0 (83.0, 98.0)	Single Night: 83.0 (76.0, 87.0) Averaged Over Multiple Nights: 85.0 (78.0, 89.0)	Single Night: 0.940 (0.870, 100.0) Averaged Over Multiple Nights: 0.950 (0.900 0.980)	Single Night: 5.3 (NR) Averaged Over Multiple Nights: 6.00 (NR)	Single Night: 0.12 (NR) Averaged Over Multiple Nights: 0.12 (NR)
Rofail, 2010[122]	Radical Set Home	AHI ≥5 NR	Single Night: 63.0 (66.0, 86.0) Averaged Over Multiple Nights: 77.0 (63.0, 91.0)	Single Night: 83.0 (74.0, 80.0) Averaged Over Multiple Nights: 89.0 (80.0, 98.0)	Single Night: 0.800 (0.690, 0.910) Averaged Over Multiple Nights: 0.810 (0.720, 0.900)	Single Night: 3.70 (NR) Averaged Over Multiple Nights: 7.20 (NR)	Single Night: 0.45 (NR) Averaged Over Multiple Nights: 0.26 (NR)
Rofail, 2010[122]	Radical Set Home	AHI ≥30 NR	Single Night: 90.0 (86.0, 96.0) Averaged Over Multiple Nights: 90.0 (87.0, 97.0)	Single Night: 88.0 (75.0, 94.0) Averaged Over Multiple Nights: 85.0 (73.0, 92.0)	Single Night: 0.910 (0.820, 0.990) Averaged Over Multiple Nights: 0.910 (0.830, 0.980)	Single Night: 7.50 (NR) Averaged Over Multiple Nights: 6.00 (NR)	Single Night: 0.11 (NR) Averaged Over Multiple Nights: 0.11 (NR)

Abbreviations: AHI=apnea-hypopnea index; AUROC=area under receiver operating characteristic curve; LR=likelihood ratio; Neg=negative; NR=not reported; PM=portable monitor; Pos=positive; PSG=polysomnography.

Appendix E Table 11. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Sham CPAP (KQ 4)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Arias, 2005[128] Cross-over	Total (37) nCPAP first (14) Sham nCPAP first (13)	NR	No	Spain	12 active; 12 sham	52	0	NR	31	44	NR	Mild to severe	0; 0	Fair
Arias, 2008[129] Cross-over	Total (30)* CPAP 1st (13) Sham 1st (12)	Unclear	No	Spain	12 active 12 sham	52	0	NR	31	44	>11 required	Mild to severe	0; 0	Fair
Barbe, 2001[130] Parallel	nCPAP (29) Sham CPAP (26)	Sleep clinic	No	Spain	6	52-54	9	NR	29	54-57	7	Severe	NR 0	Fair
Bardwell, 2007[131] Parallel	CPAP (12) Sham CPAP (12)	Ads, word of mouth	No	United States	2	44-51	13	NR	30-31	RDI 59	NR	Mod to severe	NR NR	Fair
Campos-Rodriguez, 2006[132] Parallel	CPAP (36) Sham CPAP (36)	Sleep center	No	Spain	4	55-58	35-44	NR	34-36	58-60	14-15	Mild to severe	100%;NR†	Fair
Chasens, 2014[287] Parallel	CPAP (12) Sham CPAP (11)	Community	No	United States	4	56 (34-80)	39	52	36	39	11	Mod to severe	NR; NR	Fair
Chong, 2006[134] Parallel	CPAP (19) Sham CPAP (20)	Ads, referrals	No	United States	3	78	26	5	24-25	RDI 26-31	8-9	Mild to severe	NR 0	Fair
Coughlin, 2007[135] Cross-over	Total (35) CPAP first (18) Sham first (17)	Sleep center	No	United Kingdom	6 active; 6 sham	49	0	NR	36	RDI 39.7	13.8	Mod to severe	79 0	Good
Cross, 2008[136] Cross-over	Total (29) CPAP first (15) Sham CPAP first (14)	NR	No	United Kingdom	6 active; 6 pbo	48	4	NR	37	63	NR	Mod to severe	NR; 0	Fair
Durán-Cantolla, 2010[137] Parallel	CPAP (169) Sham (171)	Referrals to 11 general hospitals	No	Spain	12	52-53	19	NR	32	43 to 45	10	Mod to severe	100 per GP, but 64 vs. 56 from ABPM; NR	Good
Egea, 2008[138] Parallel	Overall‡ CPAP (35) Sham CPAP (38)	Referral from cardiology to sleep center	No	Spain	12	63-64	4-9	NR	31-32	35-43	7-8	Mild to severe	NR 100	Fair

Appendix E Table 11. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Sham CPAP (KQ 4)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Haensel, 2007[139] Parallel	CPAP (25) Sham CPAP (25)	Advertisements, word of mouth, referrals	No	United States	2	49	20	40	33	58-64	NR	Mod to severe	14 0	Fair
Hoyos, 2012[140] Parallel	CPAP (34) Sham CPAP (31)	Sleep clinics	No	Australia	12	46-51	0	NR	31-32	39-42	10	Mod to severe	34; NR	Fair
Hui, 2006[141] Parallel	nCPAP (28) Sham CPAP (28)	Respiratory clinic	No	Hong Kong	12	51	23	NR	27	31	11	Mild to severe	50 NR	Fair
Jenkinson, 1999[142] Hack, 2000[143] Parallel	nCPAP (54) Sham nCPAP (53)	Referred to sleep clinic	No	United Kingdom	4	48-50 (33-71)	0	NR	35	ODI (>4%): 36-38	16-17	Mild to severe	19 NR	Fair
Jones, 2013[144] Cross-over	Total (53)[§] CPAP first (25) Sham CPAP first (27)	Sleep medicine department	No	United Kingdom	12 CPAP; 12 sham	46	35	NR	Median 30	Median 31	Median 13	Mod to severe	NR NR	Fair
Kushida, 2012[145] Parallel APPLES	CPAP (558) Sham (547)	Sleep Clinics (5 hospitals)	No	United States	24	51-52	34-35	24	32	40-41	10	Mild to severe	NR 0	Fair
Lam, 2010[146] Parallel	nCPAP (31) Sham nCPAP (30)	Sleep center	No	Hong Kong	1	46	0	NR	28	40	10-11	Mod to severe	NR NR	Fair
Lee, 2011[147] Parallel	Total (38) CPAP (17) Sham CPAP (21)	Ads and word of mouth	No	United States	3	48-49	NR	11	28-29	30-33	7-10	Mild to severe	5; 0	Fair
Loredo, 1999[148] Parallel	Total (48)[¶] CPAP (23) Sham CPAP (18)	Ads, word of mouth, community MD referrals	No	United States	1	47-50 (30-65)	20	NR	30-33	RDI 44-56	NR	Mod to Severe	0; 0	Fair[148]; Poor for KQ 5[292,293]
Loredo, 2006[149] Parallel	CPAP (22) Sham (19)[¶]	Ads and sleep labs	No	United States	*2*	48	17	NR	32	58-66	12	Mod to severe	NR; 0	Fair
Malow, 2008[150] Parallel	Total (35) CPAP (22) Sham CPAP (13)	Epilepsy clinic	No	United States	10 overall; 2 nights for AHI	42	43	NR	32-35	16-19	NR	Mild to severe	22%; NR	Fair
Marshall, 2005[151] Cross-over	Total (31) CPAP first (15) Sham first (16)	Sleep clinics	No	New Zealand	3 active; 3 sham	51 (25-67)	24	NR	32	21.6	13	Mild to mod	NR NR	Good

Appendix E Table 11. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Sham CPAP (KQ 4)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Mills, 2006[153] Parallel	nCPAP (17) Sham (16)[**]	Ads and referrals	No	United States	2	48-49	15	NR	32	61-65	NR	Mild to severe	36; 0	Fair
Montserrat, 2001[154] Parallel	CPAP (24) Sham CPAP (24)	Sleep clinic	No	Spain	6	54 (28-77)	NR	NR	30-34	54	16-17	Mod to severe	NR 0	Fair
Neikrug, 2014[155] Parallel	CPAP (19) Sham nCPAP (19)	Neurologist[††] referral and volunteer	No	United States	3	67-68	32	NR	27-28	22	NR	Mild to severe	NR; NR	Fair
Nguyen, 2010[157] Parallel	nCPAP (10) Sham nCPAP (10)	Sleep clinic	No	United States	12	53 (42-65)	10	40	30	32-39	NR	Mod to Severe	100 0	Fair
Norman, 2006[156] Parallel	CPAP (18) Sham CPAP (15)[‡‡]	Ads and word-of-mouth referral	No	United States	2	49-50	15	36	30-32	54-66	12	Mod to severe	NR; 0	Fair for AHI; Poor for BP
Pepperell, 2002[159] Kohler, 2008[160] Parallel	CPAP (59) Sham CPAP (59)	Referred by ENTs, GPs, or consultants	No	United Kingdom	4	50-51	0	NR	35	NR	16	Mild to severe	19; NR	Fair
Phillips, 2011[161] Cross-over	Total (38) CPAP first (18) Sham CPAP first (19)	Referrals from tertiary clinics	No	Australia	8 active; 8 sham	49	11	NR	32	38	10	Mod to severe	32; NR	Fair; Poor for harms
Robinson, 2006[162] Cross-over	Total (35) CPAP first (18) Sham first (17)	Sleep center	No	United Kingdom	4 active; 4 sham	54	11	NR	33	ODI: median 28	5.3	Mild to severe	100; NR	Fair
Siccoli, 2008[164] Parallel	CPAP (51) Sham CPAP (51)	Sleep center	No	United Kingdom	4	48	0	NR	35-36	NR	15-16	Mod to severe	NR; NR	Fair
Smith, 2007[163] Cross-over	Total (24) CPAP first (11) Sham first (13)	Cardiology clinics	No	United Kingdom	6 active; 6 sham	61	12	NR	31	36	10	Mod to severe	42 100	Fair
Weaver, 2012[166] Parallel	CPAP (141)[§§] Sham CPAP (140)	Respiratory Clinics	No	US and Canada	8	50-52	37-45	16-17	33-34	13	15	Mild to mod	40 2	Fair

Appendix E Table 11. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Sham CPAP (KQ 4)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Weinstock, 2012[167,289] Cross-over	Total (50) CPAP first (25) Sham CPAP first (25)	Sleep clinics, prior studies and ads	No	United States	8 active; 8 sham	53-54	58	40	38-39	32-44	NR	Mod to severe	NR; NR	Fair
West, 2007[168] West, 2009[169] Parallel	CPAP (21) Sham CPAP (21)	Sleep center	No	United Kingdom	12	55-58	0	NR	37	NR	14-15	Mild to severe	NR NR	Fair

* Not clear how many people were randomly assigned to each group first; 5 dropouts—unclear how many from each group.
† those with NYHA class III-IV HF were excluded.
‡ The overall study included some subjects with CSA. The numbers randomized who had OSA only was NR; the study reported number of completers who had OSA only (CPAP, 20 vs. Sham CPAP, 25)
§ 1 person dropped out before beginning a treatment, but unclear if it was before or after randomization and unclear which group they were in
‖ 48 randomized but unclear how many to each group. 23 and 18 completed.
¶ The study also had a sham+oxygen (N=22) arm. These Ns and baseline characteristics are for completers
** Study also had a sham+oxygen arm (17)
†† Patients with Parkinson's
‡‡ Study had a third arm. It was a CPAP device that only delivered oxygen (n=13).
§§ These are the numbers randomized including the post-randomization drop-outs. 42 participants withdrew before exposure to CPAP or sham and were excluded from all analyses. Ns randomized and exposure were: active CPAP =121 and sham CPAP= 118. All characteristics are for those randomized and exposed.

Abbreviations: ABPM=ambulatory blood pressure monitor; AHI=apnea-hypopnea index; APPLES=Apnea Positive Pressure Long-term Efficacy Study; BMI=body mass index; CPAP=continuous positive airway pressure; CSA=central sleep apnea; dur=duration; ENT=otolaryngologist; ESS=Epworth Sleepiness Scale; F=female; G=group; GP=general practitioner; HF=heart failure; HTN=hypertension; mod=moderate; N=sample size; nCPAP=nasal continuous positive airway pressure; NR=not reported; NYHA=New York Heart Association; ODI=oxygen desaturation index; OSA=obstructive sleep apnea; pbo=placebo; pts=patients; RDI=respiratory disturbance index; RF=radiofrequency; SD=standard deviation; tx=treatment; wks=weeks.

Appendix E Table 12. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Control (KQ 4)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Ballester, 1999[170] Parallel	CPAP (68) Usual Care (37)	NR	No	Spain	12	53	12	NR	32	56	12	Mod to severe	NR NR	Fair
Barbe, 2010[171] Parallel	CPAP (178) conservative treatment for HTN (181)	Sleep clinics	No	Spain	52	55-56	15-18	NR	32-33	43-49	6	Mod to Severe	100 NR	Fair
Barbe, 2012[172] Parallel	CPAP (357) Control (366)	Teaching hospitals	No	Spain	Median: 208[*]	52	12-16	NR	31	35-42	7	Mod to severe	50-53; NR	Fair
Barnes, 2004[173] Cross-over	CPAP (97)[†] Placebo (98)	Referrals	No	Australia	12 active; 12 placebo	47	20	NR	31	21.3	10.7	Mild to mod	15; NR	Good
Craig, 2012[174] Parallel	CPAP (195) Standard Care[‡] (196)	Sleep clinics	No	United Kingdom and Canada	24	58	22-21	NR	32-33	ODI >4% dips/hr: 9-10	8 (4)	NR[§]	76-77; NR	Fair
Engleman, 1998[175] Cross-over	Total (23) CPAP first (10) Placebo(13)	Sleep center	No	United Kingdom	4 active; 4 pbo	47	9	NR	30	43	12	Mod to severe	NR	Fair
Engleman, 1999[176] Cross-over	Total (37) CPAP first (NR) Oral Placebo first (NR)	Sleep clinic	No	United Kingdom	4 active; 4 pbo	44	38	NR	30	10	13	Mild only	NR NR	Fair
Faccenda, 2001[177] Cross-over	Total (71) CPAP first (35) Pbo capsule first (36)	Sleep center	No	United Kingdom	4 active; 4 pbo	Median 50 (29-72)	18	NR	Median 30	Median 35	Median 15	Mod to severe	0 NR	Fair
Gottlieb, 2014[178] Parallel HeartBEAT	CPAP+usual care[‖] (106) Usual care alone (106)[¶]	Cardiology practices	Yes, Berlin[#]	United States	12	63	26	20	34	25	8-10	Mod to severe	89 NR	Good
Ip, 2004[179] Parallel	CPAP (14) No treatment (14)	Sleep lab	No	Hong Kong	4	43 (21-62)	0	NR	29	45-48	11	Mod to Severe	0; 0	Fair
Lam, 2007[180] Parallel	CPAP (34)[**] Usual care (33)[††]	Sleep center	No	Hong Kong	10	45-47	22	NR	27	21.4	12	Mild to severe	19 NR	Fair
Martinez-Garcia, 2013[181] Parallel HIPARCO	CPAP (98) No CPAP (96)	HTN clinical units	No	Spain	12	56	31	NR	34	40	9	Mod to severe	100 (resist-ant HTN)[‡‡] NR	Good

Appendix E Table 12. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Control (KQ 4)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
McArdle, 2001[152] Cross-over	Total (23) CPAP first (NR) Pbo capsule first (NR)	Sleep center	No	United Kingdom	4 active; 4 pbo	53	13	NR	31	Median 40	Median 14	Mod to severe	NR; NR	Fair
McMillan, 2014[182] Parallel	CPAP + Best Supportive Care (BSC) (140) BSC only (138)	Sleep centers (14)	No	UK	52	71 (66-76)	18	4	34	28-29	12	Mild to severe	73; 6	Good
Pamidi, 2015[158] Parallel	CPAP (26) Oral placebo (13)	Ads	No	United States	2	54-55	23-38	50-62	33-37	34-39	10-11	Mild to severe	0-19; NR	Fair
Redline, 1998[183] Parallel	nCPAP (59) Conservative therapy[§§] (52)	Ads and referrals	No	United States	8-12	48	48	38	32-33	RDI 13	10-11	Mild to mod	NR; 0	Fair
Ruttanaumpawan, 2008[184] Kaneko, 2003[185] Parallel	CPAP (19) Usual care (14)	HF clinic	Yes, ESS	Canada	4	59-61	9	NR	30-32	36-51	NR	Mod to severe	42-58; 100	Fair
Tomfohr, 2011[186] Parallel	CPAP (34) Placebo CPAP (37)	Ads and referrals	No	United States	3	48	14	14	29-31	32-39	9-11	Mild to severe	NR; NR	Fair
Toukh, 2012[165] Cross-over	Total (13) CPAP first (NR) No CPAP first (NR)	Sleep center	No	Canada	2 CPAP; 2 no treatment	46 (33-61)	38	NR	36	NR	NR	Severe	NR; NR	Fair
Usui, 2005[187] Parallel	CPAP (8) Control (9)	NR	NR	Canada	4	52-55	12	NR	30-31	33-NR	NR	Mod to severe	47% 100%	Fair

[*] Followup was "time until a CVD event, loss to followup or the end of the study" and ranged from 0 to 5.38 years, with a median of 4.0 years (*IQR= 2.19-4.38).
[†] Study also had an MAD arm. Because 6 different orders were possible, they did not list out individuals' actual order. Numbers represent the number of people that started treatment in that arm. 104 participants total; 80 completed all three arms
[‡] One followup visit with a physician between randomization and the final visit at six months.
[§] Had to have >7.5 oxygen desaturations per hour of >4%...but insufficient daytime symptoms associated with OSA to warrant CPAP therapy. This was made based on discussion with physician based on benefits of CPAP versus potential lifelong nightly usage of CPAP.
[‖] Usual care was "healthy lifestyle and sleep education"
[¶] Study also had an oxygen+usual care arm (N=106)
[#] Eligible patients were required to have Berlin questionnaire score of 2 or 3 and established CAD or multiple CVD risk factors
[**] Study also has a MAD arm
[††] Authors call it "mild to moderate," but they allowed AHI up to 40, and the range of included patients included some with severe OSA
[‡‡] BP remained above goal despite at least 3 antihypertensive medications

Appendix E Table 12. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Control (KQ 4)

[§§] Conservative therapy for all patients consisted of sleep hygiene counseling, weight loss referrals for overweight patients, and nasal steroid spray for those with nasal congestion. Control participants also received nasal dilator strips.

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; BSC=best supportive care; CAD=coronary artery disease; CPAP=continuous positive airway pressure; CVD=cardiovascular disease; dur=duration; ESS=Epworth Sleepiness Scale; F=female; G=group; HeartBEAT=Heart Biomarker Evaluation in Apnea Treatment; HF=heart failure; HTN=hypertension; MAD=mandibular advancement device; mod=moderate; N=sample size; nCPAP=nasal continuous positive airway pressure; NR=not reported; ODI=oxygen desaturation index; OSA=obstructive sleep apnea; pbo=placebo; pts=patients; RDI=respiratory disturbance index; RF=radiofrequency; SD=standard deviation; tx=treatment; wks=weeks.

Appendix E Table 13. Characteristics of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices (KQs 4 and 5)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Aarab, 2011[189] Parallel	MAD (20) Intraoral Placebo Device (19)[*]	Sleep clinic	No	The Netherlands	24	52 (including drop-outs)	27	NR	29	20	11	Mild to Mod	NR NR	Fair
Andren, 2013[188] Parallel	MAD (36) Intraoral Sham/Placebo Device (36)	Sleep clinics	No	Sweden	12	57-59	17-25	NR	29-30	23-24	11	Mild-Severe	100 NR	Fair
Barnes, 2004[173] Cross-over	MAD[†] (99) Placebo (98)	Referrals	No	Australia	12 CPAP; 12 MAD; 12 placebo	47	20	NR	31	21	11	Mild to mod	15; NR	Good
Bloch. 1999[214] Cross-over	Total (24) MAD Monobloc first (8) MAD Herbst first (8) No treatment first (8)	NR	No	Switzerland	1	51	NR	NR	27	27	12	Mild to severe	NR	Fair
Durán-Cantolla, 2015[36] Cross-over	Total (42) MAD first (NR) Sham MAD first (NR)	Sleep clinic	No	Spain	12 active; 12 sham	47	21	NR	28	15	12	Mild to mod	NR	Good
Johnston, 2002[195] Cross-over	Total (21) MAD first (13) Sham MAD first (8)	Sleep clinic	No	Ireland	4-6 active; 4-6 sham	55 (35-64)	19	NR	32	32	14	Mild to severe	NR 0	Fair
Lam, 2007[180] Parallel	MAD[‡] (34) Usual care[§] (33)	Sleep center	No	Hong Kong	10	45-47	22	NR	27	21	12	Mild to severe[‖]	19 NR	Fair
Naismith, 2005[192] Gotsopoulos, 2002[193] Gotsopoulos, 2004[194]	Total (67) MAD first (35) Sham MAD first (32)	Sleep clinic	No	Australia	4 active; 4 sham	48	19	NR	29	26-28	11	Mild to severe	NR NR	Good
Petri, 2008[191] Parallel	MAD (33) Sham MAD (30) No tx (30)	ENT clinic sleep lab	No	Denmark	4	46-50	18	NR	31	35	11	Mild to severe	NR NR	Fair

Appendix E Table 13. Characteristics of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices (KQs 4 and 5)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Quinnell, 2014[197] Cross-over	Total (90) SP1 - MAD (23) SP2 - MAD (22) bMAD (23) No tx (22)	Sleep center	No	United Kingdom	6 active 4 no tx	51 (26-80)	20	NR	31	14	12	Mild to mod	26 NR	Fair

* This study also a CPAP arm

‖ Study also had a CPAP arm. Because 6 different orders were possible, they did not list out individuals' actual order. Numbers represent the number of people that started treatment in that arm. 104 participants total; 80 completed all three arms

‡ This study also a CPAP arm

§ Usual care = conservative measures - sleep hygiene and weight loss advice (if applicable)

‖ Authors call it "mild to moderate," but they allowed AHI up to 40, and the range of included patients included some with severe OSA

Abbreviations: AHI=apnea-hypopnea index; bMAD=fully-bespoke mandibular advancement device; BMI=body mass index; CPAP=continuous positive airway pressure; dur=duration; ENT=otolaryngology; ESS=Epworth Sleepiness Scale; F=female; G=group; HF=heart failure; HTN=hypertension; MAD=mandibular advancement device; mod=moderate; N=sample size; NR=not reported; OSA=obstructive sleep apnea; pbo=placebo; pts=patients; RF=radiofrequency; SD=standard deviation; SP=SleepPro; tx=treatment; wks=weeks.

Appendix E Table 14. Characteristics of Included Randomized, Controlled Trials That Evaluated Surgical Interventions (KQ 4)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Bäck, 2009[198] Parallel	Soft palate RF surgery (17) Sham surgery (15)	ENT head and neck surgical unit	No	Finland	16-24	NR (NR)	0	NR	26-29	11-12	8-10	Mild only	NR NR	Good
Browaldh, 2013[199] Parallel SKUP3	UPPP (33) No treatment (34)	ENT clinic	No	Sweden	Median 28 (range 20-58)	42-43 (NR)	9	NR	28	53	13	Mod to severe	NR 0	Good
Dixon, 2012[200] Parallel	Bariatric Surgery* (30) Conventional Weight loss program† (30)‡	Sleep clinics	No	Australia	104	47-50 (SD 8-9)	40-43	NR	44-46	57-65	NR	Mod to severe	NR; NR	Fair
Ferguson, 2002[201] Parallel	LAUP (21) No treatment (25)	NR	No	Canada	varied§	45 (31-65)	24	NR	32	16-19	10-11	Mild to Mod	NR; NR	Fair
Koutsourelaski, 2008[202] Parallel	Septoplasty (27) Sham sugery (22)	Referrals to sleep center	No	Greece	12-16	38-39	37-41	NR	30	31-32	13-14	Mild to severe	NR NR	Fair
Woodson, 2003[203] Parallel	RF surgery (30) Sham surgery (30)	Ads, referrals	No	United States	8	49 (NR)	22	NR	28-29	15-21	12-13	Mild to mod	NR NR	Fair

* Surgical intervention: Two weeks of VLED prior to placement of an LAGB (LAP-BAND System) by one of three experienced surgeons within one month of randomizations.
† Both groups were provided with auto titrating CPAP equipment.
‡ Weight loss intervention: Individualized dietary, physical activity and behavioral programs. Advice regarding physical activity encouraged walking and 200 minutes per week of structured activity, including moderate-intensity aerobic activity and resistance exercise. Dietary advice included a planned daily deficit of 500 kcal from estimated energy requirements. All participants were offered an initial intensive very low energy dietary program (VLED, Optifast, Nestle-Australia) with the meal replacements provided. The VLED were available for continued or intermittent use throughout the study.
§ Duration was 3 months after last LAUP procedure (since multiple procedures were allowed/done); 6 months after baseline for control arm. Final evaluation was performed 15.4 months after BL in treatment (which was 7.2 months after last LAUP procedure) and 8.2 months after BL in control.

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; CPAP=continuous positive airway pressure; dur=duration; ENT=otolaryngology; ESS=Epworth Sleepiness Scale; F=female; G=group; HF=heart failure; HTN=hypertension; LAGB=laparoscopic adjustable gastric band; LAUP=laser assisted uvulopalatoplasty; mod=moderate; N=sample size; NR=not reported; OSA=obstructive sleep apnea; pbo=placebo; pts=patients; RF=radiofrequency; tx=treatment; VLED=very low energy diet; wks=weeks.

Appendix E Table 15. Characteristics of Included Randomized, Controlled Trials That Evaluated Weight Loss, Diet, and Exercise Programs (KQ 4)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Desplan, 2013[204] Parallel	Inpatient individualized exercise training (13) Standard health education (13)	NR	No	France	4	NR (35-70)	NR	NR	30-31	40-41	11	Mod to severe	NR; NR	Fair
Foster, 2009[205] Kuna, 2013[206] Sleep AHEAD Parallel	Intensive lifestyle intervention* (125) Diabetes support and education (139)	Multiple, inc ads, open screenings, and prover referrals	Partially†	United States	208	61 (NR)	59	27	37	23	NR	Mild to severe	NR	Good
Johannson, 2009[207] Parallel	Very low energy diet (30) Usual diet (33)	Sleep clinic database	No	Sweden	9	49 (33-61)	0	NR	35	37	8	Mod to severe	NR	Good for AHI; Fair for ESS
Kline, 2012[208]; Kline, 2013[209] Parallel	Exercise Training‡ (27) Stretching control (16)	Sleep clinics and ads	No	United States	12	47 (NR)	40	26	35	24-32	7-11	Mod to severe	NR NR	Fair
Moss, 2014[210] Parallel	Lifestyle intervention§ (30) Advice-only control (30)	Sleep clinics	No	United Kingdom	12 active; 26 total inc followup	NR	NR	NR	39-40	2‖	5	Controlled mod to severe	NR; 0	Fair
Tuomilehto, 2009[211] Tuomilehto, 2010[212] Tuomilehto, 2013[213] Parallel	VLCD (12 wks) + supervised lifestyle (52 wks) (40) Usual care (routine lifestyle guidance) (41)	Primary care referrals to respiratory clinic	No	Finland	52 active; 260 total inc followup	51-52 (NR)	23	NR	31-33	9-10	10	Mild	41 NR	Fair

* Consisted of portion-controlled diet, physical activity, and group behavioral weight loss intervention

† Efforts were made to enroll individuals with undiagnosed OSA using a symptom questionnaire. Because almost all of the first 80 participants had OSA upon polysomnography, the symptom screen was dropped as an eligibility criterion.

‡ Moderate intensity exercise training program meeting 4x/week for 12 weeks; 150 min/wk of mod-intensity aerobic activity, followed by resistance training twice/week

§ Supervised individualized exercise sessions, cognitive-behavioral psychoeducation, dietary education and diet diary

‖ All patients were using CPAP for at least 6 months prior to study start.

Abbreviations: AHEAD=Action for Health in Diabetes; AHI=apnea-hypopnea index; BMI=body mass index; CPAP=continuous positive airway pressure; dur=duration; ESS=Epworth Sleepiness Scale; F=female; G=group; HF=heart failure; HTN=hypertension; inc=including; min=minutes; mod=moderate; N=sample size; NR=not reported; OSA=obstructive sleep apnea; pbo=placebo; pts=patients; RF=radiofrequency; tx=treatment; VLCD=very low calorie diet; wks=weeks.

Appendix E Table 16. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Any Comparator Reporting a Health Outcome (KQ 5)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Arias, 2005[128] Cross-over	Total (37) nCPAP first (14) Sham nCPAP first (13)	NR	No	Spain	12 active; 12 sham	52 (NR)	0	NR	31	44	NR	Mild to severe	0; 0	Fair
Ballester, 1999[170] Parallel	CPAP (68) Usual Care (37)	NR	No	Spain	12	53	12	NR	32	56	12	Mod to severe	NR NR	Fair
Barnes, 2004[173] Cross-over	CPAP[*] (97) Placebo (98)	Referrals	No	Australia	12 CPAP; 12 placebo	47 (NR)	20	NR	31	21.3	10.7	Mild to mod	15; NR	Good
Barbe, 2001[130] Parallel	nCPAP (29) Sham CPAP (26)	Sleep clinic	No	Spain	6	52-54	9	NR	29	54-57	7	Severe	NR 0	Fair
Barbe, 2012[172] Parallel	CPAP (357) Control (366)	Teaching hospitals	No	Spain	Median: 208[†]	52 (SD11)	12-16	NR	31	35-42	7	Mod to severe	50-53; NR	Fair
Craig, 2012[174] Parallel	CPAP (195) Standard Care (196)[‡]	Sleep clinics	No	United Kingdom and Canada	24	58 (SD 7)	22-21	NR	32-33	ODI >4% dips/hr: 9-10	8 (4)	NR[§]	76-77; NR	Fair
Durán-Cantolla, 2010[137] Parallel	CPAP (169) Sham (171)	Referrals to 11 general hospitals	No	Spain	12	52-53	19	NR	32	43 to 45	10	Mod to severe	100 per GP, but 64 vs. 56 from ABPM; NR	Good
Egea, 2008[138] Parallel	Overall[‖] CPAP (35) Sham CPAP (38)	Referral from cardiology to sleep center	No	Spain	12	63-64	4-9	NR	31-32	35-43	7-8	Mild to severe	NR 100	Fair
Engleman, 1994[216] Cross-over	Total (35)[¶] CPAP first (17) Oral placebo first (15)	Referred due to symptoms	No	United Kingdom	4 active 4 pbo	49	19	NR	33	28	NR	Mild to severe	NR; NR	Fair
Engleman, 1997[217] Cross-over	Total (18) CPAP first (10) Oral placebo first (8)	Referral to sleep clinic	No	United Kingdom	4 active, 4 pbo	52	25	NR	30	11	14	Mild only	NR; NR	Fair
Engleman, 1998[175] Cross-over	Total (23) CPAP first (10) Placebo(13)	Sleep center	No	United Kingdom	4 active 4 pbo	47	9	NR	30	43	12	Mod to severe	NR	Fair

Appendix E Table 16. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Any Comparator Reporting a Health Outcome (KQ 5)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Engleman, 1999[176] Cross-over	Total (37) CPAP first (NR) Oral Placebo first (NR)	Sleep clinic	No	United Kingdom	4 CPAP; 4 placebo	44	38	NR	30	10	13	Mild only	NR NR	Fair
Faccenda, 2001[177] Cross-over	Total (71) CPAP first (35) Pbo capsule first (36)	Sleep center	No	United Kingdom	4 active; 4 pbo	Median50 (29-72)	18	NR	Median 30	Median 35	Median 15	Mod to severe	0 NR	Fair
Gottlieb, 2014[178] Parallel HeartBEAT	CPAP+usual care[#] (106) Usual care alone (106)[**]	Cardiology practices	Yes, Berlin[i]	United States	12	63	26	20	34	25	8-10	Mod to severe	89 NR	Good
Haensel, 2007[139] Parallel	CPAP (25) Sham CPAP (25)	Ads, word of mouth, referrals	No	United States	2	49	20	40	33	58-64	NR	Mod to severe	14 0	Fair
Hoyos, 2012[140] Parallel	CPAP (34) Sham CPAP (31)	Sleep clinics	No	Australia	12	46-51 (SD 10-12)	0	NR	31-32	39-42	10	Mod to severe	34; NR	Fair
Jenkinson, 1999[142] Hack, 2000[143] Parallel	nCPAP (54) Sham nCPAP (53)	Referred to sleep clinic	No	United Kingdom	4	48-50 (33-71)	0	NR	35	ODI (>4%): 36-38	16-17	Mild to severe	19 NR	Fair
Kushida, 2012[145] Batool-Anwar, 2016[288] Parallel APPLES	CPAP (558) Sham (547)	Sleep Clinics (5 hospitals)	No	United States	24	51-52	34-35	24	32	40-41	10	Mild to severe	NR 0	Fair
Lam, 2007[180] Parallel	CPAP (34)[††] Usual care[‡‡] (33)	Sleep center	No	Hong Kong	10	45-47	22	NR	27	21.4	12	Mild to severe[§§]	19 NR	Fair
Lee, 2011[147] Parallel	Total (38) CPAP (17) Sham CPAP (21)	Ads and word of mouth	No	United States	3	48-49	NR	11	28-29	30-33	7-10	Mild to severe	5; 0	Fair
Lim, 2007[215] Parallel	nCPAP (17) Sham CPAP (14)	Ads, word of mouth, referrals	No	United States	2	47-49	NR	NR	31	64-66	11-13	Mod to severe	NR; 0	Fair
Malow, 2008[150] Parallel	Total (35) CPAP (22) Sham CPAP (13)	Epilepsy clinic	No	United States	10 overall; 2 nights for AHI	42 (NR)	43	NR	32-35	16-19	NR	Mild to severe	22%; NR	Fair

Appendix E Table 16. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Any Comparator Reporting a Health Outcome (KQ 5)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
McMillan, 2014[182] Parallel	CPAP + Best Supportive Care (BSC) (140) BSC only (138)	Sleep centers (14)	No	UK	52	71 (66-76)	18	4	34	28-29	12	Mild to severe	73; 6	Good
Marshall, 2005[151] Cross-over	Total (31) CPAP first (15) Sham first (16)	Sleep clinics	No	New Zealand	3 active; 3 sham	51 (25-67)	24	NR	32	21.6	13	Mild to mod	NR NR	Good
Montserrat, 2001[154] Parallel	CPAP (24) Sham CPAP (24)	Sleep clinic	No	Spain	6	54 (28-77)	NR	NR	30-34	54	16-17	Mod to severe	NR 0	Fair
Neikrug, 2014[155] Parallel	CPAP (19) Sham nCPAP (19)	Neurologist‖‖ referral and volunteer	No	United States	3	67-68	32	NR	27-28	22	NR	Mild to severe	NR; NR	Fair
Nguyen, 2010[157] Parallel	nCPAP (10) Sham nCPAP (10)	Sleep clinic	No	United States	12	53 (42-65)	10	40	30	32-39	NR	Mod to Severe	100 0	Fair
Phillips, 2011[161] Cross-over	Total (38) CPAP first (18) Sham CPAP first (19)	Referrals from tertiary clinics	No	Australia	8 active; 8 sham	49	11	NR	32	38	10	Mod to severe	32; NR	Fair
Redline, 1998[183] Parallel	nCPAP (59) Conservative therapy¶¶ (52)	Ads and referrals	No	United States	8-12	48	48	38	32-33	RDI 13	10-11	Mild to mod	NR; 0	Fair
Robinson, 2006[162] Cross-over	Total (35) CPAP first (18) Sham first (17)	Sleep center	No	United Kingdom	4 active; 4 sham	54 (NR)	11	NR	33	ODI: median 28	5.3	Mild to severe	100; NR	Fair
Ruttanaumpawan, 2008[184] Kaneko, 2003[185] Parallel	CPAP (19) Usual care (14)	HF clinic	Yes, ESS	Canada	4	59-61	9	NR	30-32	36-51	NR	Mod to severe	42-58; 100	Fair
Siccoli, 2008[164] Parallel	CPAP (51) Sham CPAP (51)	Sleep center	No	United Kingdom	4	48 (NR)	0	NR	35-36	NR	15-16	Mod to severe	NR NR	Fair
Smith, 2007[163] Cross-over	Total (24) CPAP first (11) Sham first (13)	Cardiology clinics	No	United Kingdom	6 active; 6 sham	61	12	NR	31	36	10	Mod to severe	42 100	Fair

Appendix E Table 16. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Any Comparator Reporting a Health Outcome (KQ 5)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Quality
Weaver, 2012[166] Parallel	CPAP (141)[##] Sham CPAP (140)	Respiratory Clinics	No	US and Canada	8	50-52 (SD 11-12)	37-45	16-17	33-34	13	15	Mild to mod	40 2	Fair
West, 2007[168] West, 2009[169] Parallel	CPAP (21) Sham CPAP (21)	Sleep center	No	United Kingdom	12	55-58	0	NR	37	NR	14-15	Mild to severe	NR NR	Fair

[*] Study also had an MAD arm. Because 6 different orders were possible, they did not list out individuals' actual order. Numbers represent the number of people that started treatment in that arm. 104 participants total; 80 completed all three arms

[†] Followup was "time until a CVD event, loss to followup or the end of the study" and ranged from 0 to 5.38 years, with a median of 4.0 years (*IQR= 2.19-4.38).

[‡] One followup visit with a physician between randomization and the final visit at six months.

[§] Had to have >7.5 oxygen desaturations per hour of >4%...but insufficient daytime symptoms associated with OSA to warrant CPAP therapy. This was made based on discussion with physician based on benefits of CPAP versus potential lifelong nightly usage of CPAP.

[‖] The overall study included some subjects with CSA. The numbers randomized who had OSA only was NR; the study reported number of completers who had OSA only (CPAP, 20 vs. Sham CPAP, 25)

[‖] 3 withdrew after start of tx but its not clear from which arm(s)

Eligible patients were required to have Berlin questionnaire score of 2 or 3 and established CAD or multiple CVD risk factors

[**] Study also had an oxygen+usual care arm (N=106)

[††] study also has a MAD arm

[‡‡] Usual care = conservative measures - sleep hygiene and weight loss advice (if applicable)

[§§] Authors call it "mild to moderate," but they allowed AHI up to 40, and the range of included patients included some with severe OSA

[‖‖] patients with Parkinson's

[¶¶] conservative therapy for all patients consisted of sleep hygiene counseling, weight loss referrals for overweight patients, and nasal steroid spray for those with nasal congestion. Control participants also received nasal dilator strips.

[##] These are the numbers randomized including the post-randomization drop-outs. 42 participants withdrew before exposure to CPAP or sham and were excluded from all analyses. Ns randomized and exposure were: active CPAP =121 and sham CPAP= 118. All characteristics are for those randomized and exposed.

Abbreviations: ABPM=ambulatory blood pressure monitor; AHEAD=Action for Health in Diabetes; AHI=apnea-hypopnea index; APPLES=Apnea Positive Pressure Long-term Efficacy Study; BMI=body mass index; CPAP=continuous positive airway pressure; CSA=central sleep apnea; CVD=cardiovascular disease; dur=duration; ESS=Epworth Sleepiness Scale; F=female; G=group; GP=general practitioner; HEARTBEAT=HeartBEAT=Heart Biomarker Evaluation in Apnea Treatment; HF=heart failure; HTN=hypertension; IQR=interquartile range; MAD=mandibular advancement device; mod=moderate; N=sample size; nCPAP=nasal continuous positive airway pressure; NR=not reported; ODI=oxygen desaturation index; OSA=obstructive sleep apnea; pbo=placebo; pts=patients; RDI=respiratory disturbance index; RF=radiofrequency; SD=standard deviation; tx=treatment; wks=weeks.

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
Arias, 2005[128]	Total (37) nCPAP first (14) Sham nCPAP first (13)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Ballester, 1999[170]	CPAP (68) Usual Care (37)	0 (0.0) 0 (0.0)	NHP domains: Emotional Reaction, mean (SE) Baseline CPAP: 28.4 (3.3) UC: 29.4 (5.0) 12 wks CPAP: 17.0 (3.0) UC: 26.4 (4.5) Between groups p=0.080 Sleep, mean (SE) Baseline CPAP: 30.1 (3.3) UC: 23.1 (3.8) 12 wks CPAP: 18.1 (3.0) UC: 16.0 (4.0) Between groups p=0.183 Physical, mean (SE) Baseline CPAP: 24.2 (2.6) UC: 25.0 (3.6) 12 wks CPAP: 15.1 (2.1) UC: 21.1 (3.2) Between groups p=0.090 Continued from above row Social isolation, mean (SE) Baseline CPAP: 14.2 (2.3) UC: 13.2 (3.0) 12 wks CPAP: 8.5 (1.8) UC: 11.2 (3.4)	Daytime function, mean (SE) Baseline CPAP: 33.9 (1.3) UC: 32.3 (1.7) 12 wks CPAP: 24.2 (1.2) UC: 29.7 (2.0) Between groups p<0.005	NR	NR	NR	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			Between groups p=0.030 NHP Domains: Pain, mean (SE) Baseline CPAP: 20.5 (3.3) UC: 20.6 (4.0) 12 wks CPAP: 14.8 (3.1) UC: 15.1 (3.9) Between groups p=0.940 Energy, mean (SE) Baseline CPAP: 34.3 (4.7) UC: 23.2 (4.6) 12 wks CPAP: 12.7 (3.3) UC: 22.2 (5.0) Between groups p<0.005					
Barbe, 2001[130]	Total (55) CPAP (29) Sham CPAP (26)	0 (0.0) 0 (0.0)	FOSQ, mean (SE) Baseline CPAP: 102 (3) Sham: 107 (3) 6 wks CPAP 108 (2) Sham: 110 (2) Change from BL CPAP: 7 (2) Sham: 3 (3) Between group: p>0.2 SF-36 PCS, mean (SE) Baseline CPAP: 49 (1) Sham: 48 (1) 6 wks CPAP: 51 (1) Sham: 50 (1) Change from BL CPAP: 2 (1) Sham: 1 (1)	Hits on Steer Clear test, mean (SE) % Baseline CPAP: 5 (1) Sham: 6 (2) 6 wks CPAP: 4 (1) Sham: 5 (2) Change from BL CPAP: -1 (1) Sham:-1 (1) Between group p>0.2 Also reported: WAIS digit symbols, block design, digit span, PASAT 1-4, Trail making test A & B, Wechsler memory scale	NR	NR	NR	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			Between group: p>0.2 SF-36 MCS, mean (SE) Baseline CPAP: 51 (2) Sham: 50 (2) 6 wks CPAP: 51 (2) Sham: 52 (2) Change from BL CPAP Change: -1 (2) Sham Change: 1 (2) Between group: p>0.2						
Barbe, 2012[172]	CPAP (357) Control (366)	All-cause:* 8 (2.2) 3 (0.8) CVD-specific: 1 (0.3) 0 (0.0)	NR	NR	NR	Total: 19 (5.3) 19 (5.2) CV† Hospitalizations: 17 (4.8) 11 (3.0) Nonfatal myocardial infarction: 2 (0.6) 8 (2.2)	TIA: 2 (0.6) 5 (1.4) Non-fatal stroke: 3 (0.8) 2 (0.5)	3 (0.8) 5 (1.4)	NR
Barnes, 2004[173]	CPAP (97) Placebo (98)	0 (0.0) 0 (0.0)	FOSQ mean score, mean (SE): Baseline: 3.1 (0.1) 3.3 (0.1), p < 0.001 3.3 (0.1), p < 0.01 CPAP vs. Placebo p < 0.05	Reported: Word Pair Memory Recall; Logical Memory Test; Digit Span Backwards; Trailmaking B; Digit Symbol Substitution Task; COWAT; PVT; Stroop Color Association Test	NR	NR	NR	NR	NR
Craig, 2012[174]	CPAP (195) Standard Care (196)	1 (0.5) 0 (0.0)	MCS, Mean (SD) Baseline: 48.2 (10.4) 46.6 (11.3) 24 weeks: 52.0 (9.8)	NR	NR	Angina: 1 (0.6) 3 (1.7)	TIA: 1 (0.6) 0 (0.0)	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			48.5 (11.0) Between group difference: 2.6 (95% CI, 0.9 to 4.2; p=0.003) EQ-5D score, Mean (SD)[‡] Baseline: 0.80 (0.17) 0.75 (0.24) 24 weeks: 0.83 (0.19) 0.80 (0.22) Between group difference: +0.20 (95% CI, -0.03 to 0.06; p=0.43) SAQLI, mean (SD) Baseline: 4.9 (1.1) 4.8 (1.2) 24 weeks: 5.6 (1.0) 5.0 (1.3) Mean change (SE) 0.7 (0.1) 0.2 (0.1) Between group difference: p<0.0001			MI: 0 (0.0) 0 (0.0) PVD: 2 (1.2) 1 (0.6) AF: 6 (3.5) 7 (4.1)	Stroke: 0 (0.0) 0 (0.0)		
Durán-Cantolla, 2010[137]	CPAP (169) Sham (171)	0 (0.0) 0 (0.0)	EuroQol, mean (SD) at baseline, 6 wks, 12 wls CPAP 69 (15), 74 (14),[§] 76 (16)[‖] Sham CPAP 72 (17), 72 (16), 73 (15)	NR	NR	NR	NR	NR	NR
Egea, 2008[138]	CPAP[¶] (35) Sham CPAP (38)	0 (0.0) 1 (2.6)	OSA Only SF-36 – PCS, Mean (SE) Baseline: 41.4 (2.0) 42.0 (2.1) 12 weeks 44.9 (1.8), p = 0.10 40.7 (2.1), p = 0.41 Between group p=NS	NR	NR	Angina 0 (0.0) 1 (2.6)	NR	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			SF-36 – MCS, Mean (SE) Baseline: 46.4 (3.0) 45.8 (2.7) 12 weeks 48.8 (2.3), p = 0.40 48.7 (2.2), p = 0.27 Between group p=NS						
Engleman, 1994[216]	CPAP first (17) Oral placebo first (15)	0 (0.0) 0 (0.0)	NHP-2, 4 wks: 4.9 (SE 0.9) 7.9 (SE 0.9) Between groups p=0.002 CPAP > placebo (p<0.05) for social life, sex life, and ability to carry out domestic chores	Mental Flexibility (Trailmaking B) 66 (SE 5) 75 (SE 5) Between groups P= 0.02 Coding efficiency (Digit symbol substitution) 52 (SE 2) 51 (SE 2) Between groups P= 0.05 Vigilance (Steer Clear, N objects hit) 76 (SE 5) 81 (SE 6) Between groups P= 0.01 IQ decrement score 4.0 (SE 2.1) 7.2 (SE 2.0) Between groups P= 0.04 Concentration (PASAT 2) Between groups P= 0.02 but after adjustment for order effect, P=0.11	NR	NR	NR	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
Engleman, 1997[217]	CPAP first (8) Oral placebo first (8)	0 (0.0) 0 (0.0)	Nottingham Health Profile Part 2, total score 4 wks 3.8 (SE 1.1) 5.8 (SE 1.4) Betw groups p=NS Better compliers (mean 5 hrs/night), NHP Part 2 total score 4 wks 2.4 (SE 1.5) 6.8 (SE 2.5) Betw groups p=0.03	Reports IQ decrement, Trailmaking, SteerClear, PASAT2, RVIPT, reaction time, verbal fluency, BVRT. Only significant changes on TrailMaking B no changes on other various cognitive functioning measures	NR	NR	NR	NR	NR
Engleman, 1998[175]	CPAP first (10) Placebo (13)	0 (0.0) 0 (0.0)	NHP-2 Baseline, mean (SD) 8.0 (5.0) 4 wks, mean (SD) 5.8 (5.4) 6.3 (5.7) Between group change: -0.5 (95% CI, -2.5 to 1.5; p=NS)	No significant difference between groups on changes in the following: 30 min. SteerClear;TrailMaking B; WAIS-R performance IQ (Block Design and Digit Symbol Substitution);NART; RVIP;[#] 8-choice reaction time; PASAT;[**] Verbal fluency; BVRT[††]	NR	NR	NR	NR	NR
Engleman, 1999[176]	Total (37) CPAP first (NR) Oral Placebo first (NR)	0 (0.0) 0 (0.0)	NHP- 2 score, mean (SD) Baseline: 10.5 (4.8) 4 wks CPAP: 6.1 (4.7) 4 wks placebo: 7.3 (5.2) Between groups p = NS SF-36 Domains only: Physical Function Baseline: 75 (27) 4 wks CPAP: 84 (22) 4 wks placebo: 83 (23) Between groups p=NS	SteerClear (obstacles hit), mean (SD) Baseline: 295 (183) 4 wks CPAP: 189 (156) 4 wks placebo: 195 (158) Between groups p=NS Also reported TrailMaking A, Trailmaking B, Digit Symbol, Block	NR	NR	NR	NR	0 (0.0) 3 (8.8)

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			Mental health Baseline: 64 (19) 4 wks CPAP: 79 (16) 4 wks Placebo: 75 (15) Between groups p=NS General Health Baseline: 68 (21) 4 wks CPAP: 76 (19) 4 wks placebo: 74 (20) Between groups p=NS	Design, performance IQ, PASAT					
Faccenda, 2001[177]	Total (71) CPAP first (35) Pbo capsule first (36)	0 (0.0) 0 (0.0)	FOSQ total, mean change from baseline (SE): 12.4 (0.5) 11.6 (0.7) P=0.010	NR	NR	NR	NR	NR	NR
Gottlieb, 2014[178] HeartBEAT	CPAP+ usual care (106) Usual care alone (106)	0 (0.0) 0 (0.0)	NR	NR	0 (0.0) 0 (0.0)	Unstable angina: 0 (0.0) 1 (0.9) MI: 0 (0.0) 1 (0.9) PCI for worsening angina: 0 (0.0) 1 (0.9 AF: 1 (0.9) 0 (0.0) Arrhythmia‡‡ 0 (0.0) 1 (0.9)	Stroke: 0 (0.0) 1 (0.9)	NR	NR
Haensel, 2007[139]	CPAP (25) Sham CPAP (25)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
Hoyos, 2012[140]	CPAP (34) Sham CPAP (31)	All-cause: 0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Jenkinson, 1999[142] Hack, 2000[143]	CPAP (54) Subtherapeutic CPAP (53)	0 (0.0) 0 (0.0)	SF-36 MCS, mean (SD) Baseline: 44.8 (10.4) 43.5 (10.7) 4 wks: 55.4 (7.0) 47.8 (10.1) Between group change: p=0.002 SF36 PCS, mean (SD): Baseline: 43.7 (11.6) 42.6 (10.1) 4 wks: 49.4 (10.1) 45.5 (10.4) 5.7 (NR); p<0.001 2.9 (NR); p=0.007 Between group change: p=0.080	Measures of driving simulation	NR	NR	NR	NR	NR
Kushida, 2012[145] Batool-Anwar, 2016[288] APPLES	CPAP (558) Sham (547)	2 (0.4) 2 (0.4)	SAQLI, mean (SD) Compliance < 4 hours Baseline: 4.7 (0.8) 4.6 (0.8) 6 months: 4.7 (0.8) 4.6 (1.0) Between-group change: p≥0.05 Compliance > 4 hours Baseline: 4.7 (0.8) 4.8 (0.8) 6 months: 5.0 (0.7) 4.9 (0.7)	No difference between groups on multiple measures of neurocognitive function (Pathfinder NumberTest, Buschke Selective Reminding Test, Sustained Working Memory Test)	10 (1.8) 11 (2.0)	CV events reported as "adverse events" but not defined: 31 (5.6) 29 (5.3)	NR[§§]	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			Between-group change: p<0.05						
Lam, 2007[180]	CPAP (34) Usual care (33)	0 (0.0) 0 (0.0)	SAQLI total score, mean (SE) Baseline: 5.0 (0.1) 5.1 (0.1) 10 weeks: 5.5 (0.1) 5.0 (0.1) Between group difference: 0.77 (-1.5 to 0.4); p=0.04 SF36, mean (SEM); p-val of within group change from BL; between group change from BL vs. usual care Physical function domain, Baseline 84.7 (2.2) 82.3 (2.6) 10 weeks 88.2 (1.7); p<0.05; p<0.05 78.9 (3.6) General health domain, Baseline 48.3 (3.1) 51.2 (3.3) 10 weeks 58.9 (3.3); p<0.05; p=NS 54.8 (3) Mental health domain, Baseline 66.8 (2.5) 65.6 (2.5) 10 weeks 71.8 (2.8); p=NS; p=NS 68.0 (2.5)	NR	NR	NR	NR	NR	NR
Lee, 2011[147]	Total (38) CPAP (17) Sham CPAP (21)	0 (0.0) 0 (0.0)	NR	Measured: WAIS-III; Digit Symbol; Digit Span; Letter-Number Sequencing; Symbol Search; Brief	NR	NR	NR	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
				Visuospatial Memory Test-Rev; Hopkins Verbal Learning Test-Rev; Trail Making A/B; Digit Vigilance; Stroop Color-Word; Word Fluency					
Lim, 2007[215]	Total (46) nCPAP (17) Sham CPAP (14)	NR	NR	Reports multiple cognitive function outcomes	NR	NR	NR	NR	NR
Malow, 2008[150]	Total (35) CPAP (22) Sham CPAP (13)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Marshall, 2005[151]	Total (31) CPAP first (15) Sham first (16)	0 (0.0) 0 (0.0)	FOSQ total, mean (SE): Baseline: 12.6 (0.3) 13.6 (0.3), p < 0.01 13.3 (0.3), p=ns Btwn groups diff= 0.3 (-0.5 to 1.1) **SF36 domains** Mental health Baseline: 75 (3) 77 (2) p=NS 80 (2) p <0.05 Btwn groups diff=-3 (-10 to 3) Physical functioning Baseline: 82 (3) 81 (2) p=NS 80 (2) p=NS Btwn groups diff=1 (-3 to 6) General health Baseline: 74 (3) 76 (2) p=NS 76 (2) p=NS Btwn groups diff=0 (-6 to 7)	Psychomotor vigilance task: Mean (SE) reaction time (ms): Baseline: 264 (5) 266 (5) p=NS 259 (5) p=NS Betw groups diff=7 (-7 to 20) Mean (SE) lapses (>500 ms reaction time): Baseline: 1.3 (0.3) 3.2 (0.7) p=NS 3.3 (0.7) p=NS Betw groups diff=0.4 (-0.7 to 1.4) Errors, mean (SE): Baseline: 2.8 (0.5) 3.2 (0.7) p=NS 3.3 (0.7) p=NS Betw groups diff= -0.1 (-2.0 to 1.9)	NR	Non-fatal MI: 0 (0.0) 1 (3.2)	NR	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
McMillan, 2014[182]	Total (278) CPAP + BSC (140) BSC only (138)	NR	SAQL, baseline, mean (SD) 4.8 (1.2) 4.7 (1.2) 12 weeks, mean (SD) 5.3 (1.1) 5.0 (1.1) between groups p=0.005 52 weeks, mean (SD) 5.5 (1.1) 5.1 (1.1) between groups p=0.001 SF-36 reported in Figure only; authors report improvement on the energy and vitality subscales	No difference between groups in cognitive function measures: Digit symbol substitution Trail Making B Simple reaction time	52 weeks: 2 (3.0) 1 (1.0)	52 weeks: MI 3 (2.1) 0 (0.0) New Angina 2 (1.4) 3 (2,2) New A-fib 6 (4.3) 12 (8.7) New PVD 1 (0.3) 0 (0.0) All 12 (4.3) 15 (10.1) betw groups for all CV events p=0.72	52 weeks: Stroke 0 (0.0) 0 (0.0) “Mini-stroke” 1 (0.3) 2 (1.4) between groups for al adverse CV events p=0.72	NR	
Montserrat, 2001[154]	CPAP (24) Placebo CPAP (24)	0 (0.0) 0 (0.0)	FOSQ total, mean change from baseline (SD): 25.0 (NR); P<0.001 14.5 (NR); P=0.008 Between groups P=0.12 SF36 MCS, mean change from baseline (SD): 1.32 (NR); P=0.61 4.92 (NR); P=0.006 Between groups P=0.52 SF36 PCS, mean change from baseline (SD): 4.18 (NR); P=0.002 1.62 (NR); P=0.36 Between groups P=0.23	NR	NR	NR	NR	NR	NR
Neikrug, 2014[155]	CPAP (19) Sham CPAP (19)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
Nguyen, 2010[157]	nCPAP (10), sham CPAP (10)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Phillips, 2011[161]	Total (38) CPAP first (18) Sham CPAP first (19)	NR	FOSQ total, mean (SD): Baseline: 15.2 (3.1) 8 week, mean (SE): 16.0 (0.53) 16.7 (0.52) Between groups P=0.056	NR	NR	NR	NR	NR	NR
Redline, 1998[183]	Total (111) nCPAP (59) Conservative therapy (52)	0 (0.0) 0 (0.0)	SF-36 Energy/fatigue subscore, mean (SD) Baseline: 51.7 (19.8) 58.3 (19.0) Change from BL to 8-12 wks 10.3 (17.8) 2.3 (16.8) Between groups p<0.05	NR	NR	NR	NR	NR	NR
Robinson, 2006[162]	Total (35) CPAP first (18) Sham first (17)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Ruttanaumpawan, 2008[184]	CPAP (12) No treatment (12)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	(All pts had HF)	NR
Siccoli, 2008[164]	CPAP (51) Sham CPAP (51)	0 (0.0) 0 (0.0)	SF-36 PCS,[III] Mean (SD) Baseline 62.0 (20.0) 69.4 (21.5) 4 weeks 70.8 (18.5) P<0.0001 70.0 (18.8) P=0.68 Between groups P=0.010 SF-36 MCS, Mean (SD) Baseline 62.2 (20.2) 64.8 (21.2) 4 weeks	NR	NR	NR	NR	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			76.8 (16.2) P<0.0001 68.6 (22.7) P=0.17 Between groups P=0.002 SAQLI , Mean (SD) Baseline 3.5 (1.0) 3.8 (1.1) 4 weeks 4.4 (1.1) P<0.0001 3.8 (1.6) P=0.65 Between groups P=0.001						
Smith, 2007[163]	Total (26) CPAP first (11) Sham first (13)	0 (0.0) 0 (0.0)	MLHF Baseline: 38 (27) G1: 36 (29) G2: 34 (28) Between groups difference 1.0 (-4.3 to 6.4) P=0.70 SF36 PCS Baseline: 34 (16) G1: 34 (14) G2: 35 (14) Between groups difference -1.0 (-3.6 to 1.6) P=0.43 SF36 MCS Baseline: 51 (10) G1: 49 (12) G2: 50 (11) Between groups difference -0.5 (-4.2 to 3.2) P=0.79	NR	NR	NR	NR	NR	NR
Weaver, 2012[166]	Total (281) CPAP (141) Sham CPAP (140)	0 (0.0) 0 (0.0)	FOSQ total, unadj mean change from BL (SD): 0.98 (2.89) p=0.0005 -0.14 (2.61) p=0.57 Adj mean change from BL (SD): 0.89 (NR) -0.06 (NR) Adj diff in mean change (SE); 0.95 (0.34) Between groups p=0.006	NR	NR	NR	NR	NR	NR

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			SF-36, PCS Adj mean change from BL: 3.89 0.04 Adj between group difference in mean change from BL (SE): 3.85 (1.17) 95% CI, 1.53-6.17 p=0.001 SF-36, MCS Adj mean change from BL: 3.07 2.21 Adj between group difference in mean change from BL (SE): 0.86 (1.42) 95% CI, -1.95 -3.67 p=0.546						
West, 2007[168]	CPAP (20) Sham CPAP (22)	NR	SAQLI, mean (SD) Baseline 4.3 (1.1) 4.4 (0.9) Change from BL at 12 wks: +0.8 (1.0) +0.03 (1.2) Between-group difference (95% CI): 0.77 (-1.5 to 0.04); p=0.04	NR	NR	1 CPAP patient (5%) had emergency cardiac surgery	NR	NR	NR

* Footnote: For all-cause mortality, the authors also report an incidence density ratio: 2.6 (95% CI, 0.70-11.8; P=0.16)
† Hospitalizations were for unstable angina or arrhythmias.
‡ Authors also report the EQ-5D Health Status (Visual Analogue Score); there were no differences between groups in the total score (p=0.095).
§ P<0.001 compared with baseline; effect size (SD units) 0.31
‖ P<0.001 compared with baseline; effect size (SD units) 0.38; EuroQol scores improved significantly only in the CPAP group
¶ Sample size includes some patients who had central sleep apnea.
# Rapid visual information proecessing
** 2 second presentation rate
†† Benton visual retention test
‡‡ Per authors, one person in the control group developed "unspecified tachyarrhythmia requiring hospitalization."
§§ Authors report counts for neurological "adverse events" but do not specify how these were measured or defined: CPAP 36 events (6.5%) versus Sham 32 events (5.9%)
‖‖ Authors also report a score for the PCS and MCS components of the SF-12; results are similar to those seen on the SF-36.

Appendix E Table 17. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

Abbreviations: adj=adjusted; AF=atrial fibrillation; APPLES=Apnea Positive Pressure Long-term Efficacy Study; BL=baseline; BSC=best supportive care; btwn=between; BVRT=Benton Visual Retention Test; CBV=cerebrovascular; CI=confidence interval; COWAT=Controlled Oral Word Association Test; CPAP=continuous positive airway pressure; CV=cardiovascular; CVD=cardiovascular disease; EQ=EuroQoL; FOSQ=Functional Outcomes of Sleep Questionnaire; G=group; HeartBEAT=Heart Biomarker Evaluation in Apnea Treatment; HF=heart failure; MCS=Mental Component Score of the SF-36; IQ=intelligence quotient; MI=myocardial infarction; MLHF=Minnesota Living with Heart Failure; ms=milliseconds; MVA=motor vehicle accident; N=sample size; NART=National Adult Reading Test**;** NHP=Nottingham Health Profile; nCPAP=nasal continuous positive airway pressure; NR=not reported; NS=not significant; PASAT=Paced Auditory Serial Addition Test; PCI=percutaneous coronary intervention; PCS=Physical Component Score of the SF-36; pts=patients; PVD=peripheral vascular disease; PVT=psychomotor vigilance test; RVIP=Rapid Visual Information Processing; SAQLI=Sleep Apnea Quality of Life Index; SE=standard error; SF-36=36-Item Short Form Health Survey; TIA=transient ischemic attack; UC=usual care; WAIS=Wechsler Adult Intelligence Scale; wks=weeks.

Appendix E Table 18. Results of Included Randomized, Controlled Trials That Evaluated a Health Outcome: Bariatric Surgery, Weight Loss Programs, and Oral Surgery (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
Bäck, 2009[198]	Soft palate RF surgery (17) Sham surgery (15)	0 (0.0) 0 (0.0)	SF-36 PCS, Median (Range) Baseline: 47.2 (22.7 to 64.1) 49.4 (37.6 to 60.4) 16 weeks: 48.5 (33.0 to 67.4) 55.3 (19.1 to 63.7) Between-groups P=0.713 SF-36 MCS, Median (Range) Baseline: 53.7 (20.9 to 68.2) 51.6 (22.2 to 63.2) 16 weeks: 55.3 (19.1 to 63.7) 45.0 (28.1 to 61.6) Between groups P=0.345	NR	NR	NR	NR	NR	NR
Desplan, 2013[204] Parallel	Inpatient individualized exercise training (13) Standard health education (13)	NR	SF-36 Domains: Physical functioning, baseline: 72.7 (18.9) 70.0 (31.2) Physical functioning, 4 weeks: 92.2 (5.8); p<0.005 80.9 (16.1); p=0.29 Role limitation (physical), baseline: 36.4 (37.7) 70.5 (36.8) Role limitation (physical), 4 weeks: 86.4 (23.3); p<0.005 70.5 (36.8); p=1.00 Vitality, baseline: 38.1 (22.9) 53.2 (15.7) Vitality, 4 weeks: 76.2 (11.8); p=0.0002 52.3 (13.5); p=0.83 Role limitation (emotional), baseline: 57.6 (47.4) 54.6 (40.2) Role limitation (emotional), 4 weeks: 78.8 (30.8); p=0.13 60.6 (44.3); p=0.72	NR	NR	NR	NR	NR	NR

Appendix E Table 18. Results of Included Randomized, Controlled Trials That Evaluated a Health Outcome: Bariatric Surgery, Weight Loss Programs, and Oral Surgery (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			Mental health, baseline: 56.4 (19.8) 45.9 (15.6) Mental health; 4 weeks: 64.1 (19.0); p=0.20 49.9 (17.9); p=0.17 Social functioning, baseline: 56.7 (35.0) 66.9 (21.9) Social functioning, 4 weeks: 83.9 (12.3); p=0.02 73.3 (24.7); p=0.19						
Dixon, 2012[200] Paralell	Bariatric Surgery (30) Conventional Weight loss program (30)	0 (0.0) 0 (0.0)	SF-36 PCS: Baseline: NR 104 weeks, mean (95% CI): 48.0 (43.9 to 52.1) 44.5 (40.1 to 49.0) Change from baseline (95% CI): 12.6 (7.3 to 17.9) 3.4 (-1.6 to 8.4) Between group difference (95% CI): 9.3 (0.5 to 18.0); p=0.04 SF-36 MCS: Baseline: NR 104 weeks, mean (95% CI): 48.5 (45.5 to 51.4) 46.7 (43.9 to 49.4) Change from baseline (95% CI): 0.5 (-3.0 to 4.0) 0.8 (-2.2 to 3.8) Between group difference (95% CI); -0.3 (-5.3 to 4.8); p=0.92	NR	NR	NR	NR	NR	1 (3.3) 0 (0.0)
Ferguson, 2002[201] Parallel	LAUP (21) No treatment (25)	0 (0.0) 0 (0.0)	SAQLI (total) Baseline: 4.2 (0.8) 4.1 (1.0) Endpoint* 4.6 (0.9); p>0.05 from BL 4.3 (1.5); p>0.05 from BL Between groups p=NS	NR	NR	NR	NR	NR	NR

Appendix E Table 18. Results of Included Randomized, Controlled Trials That Evaluated a Health Outcome: Bariatric Surgery, Weight Loss Programs, and Oral Surgery (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
Foster, 2009[205] Kuna, 2013[206] Sleep AHEAD Parallel	Intensive lifestyle intervention (125) Diabetes support and education (139)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Johansson, 2009[207] Parallel	Very low energy diet (30) Usual diet (33)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Kline, 2012[208] Kline, 2013[209] Parallel	Exercise Training (27) Stretching control (16)	0 (0.0) 0 (0.0)	FOSQ-10 (total score), mean (SE) Baseline: 15.1 (0.5) 16.0 (0.6) 12 weeks: 16.7 (0.5) 16.0 (0.6) Between groups: P= NS SF-36 domains, Mean (SE) Physical Functioning: Baseline: 77.2 (4.1) 76.3 (4.8) 12 weeks: 86.1 (2.9) 76.6 (4.9) Between groups: P≤0.05 General Health: Baseline: 63.7 (3.1) 66.9 (4.3) 12 weeks: 72.4 (3.4) 68.4 (3.9) Between groups: P=NS Mental Health: Baseline: 71.7 (3.6)	No statistically significant difference between groups on the following: Psychomotor Vigilance Test (PVT), Stroop Color-Word Test (SCWT), and Trail-Making Test (TMT)	NR	NR	NR	NR	NR

Appendix E Table 18. Results of Included Randomized, Controlled Trials That Evaluated a Health Outcome: Bariatric Surgery, Weight Loss Programs, and Oral Surgery (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			74.0 (3.9) 12 weeks: 80.6 (2.5) 76.0 (3.2) Between groups: P≤0.05						
Koutsoure-laski, 2008[202] Parallel	Septoplasty (27) Sham sugery (22)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Moss, 2014[210]	Lifestyle intervention (30) Advice only (30)	NR	EuroQoL EQ-5D-3L VAS, mean (SD) Baseline: 64 (17) 58 (18) 13 weeks: 60 (20) 63 (19) Adjusted mean difference between groups: 3 (95% CI: -4 to 10) Between groups P=0.385 26-wk followup: 72 (16) 69 (18) Adjusted mean difference between groups: 9 (95% CI: 2 to 16) Between groups P=0.017	NR	NR	NR	NR	NR	NR
Tuomilehto, 2009[211] Tuomilehto, 2010[212] Tuomilehto, 2013[213]	VLCD (12 wks) + supervised lifestyle (52 wks) (40) Usual care (routine lifestyle guidance) (41)	1 (1.2) NR which arm	15D score, overall, change from BL:+0.041 +0.022 Between groups P=0.167	NR	NR	NR	NR	NR	NR
Woodson, 2003[203] Parallel	RF surgery (30) Sham surgery (30)	NR	FOSQ total, mean change from baseline (SD): 1.2 (1.6); P=0.005 0.4 (2.0); P=0.18 Between groups difference (95% CI): 0.9 (-0.1 to 1.9); P = 0.04	No difference between groups on multiple measures of reaction time measured with	NR	NR	NR	NR	NR

Appendix E Table 18. Results of Included Randomized, Controlled Trials That Evaluated a Health Outcome: Bariatric Surgery, Weight Loss Programs, and Oral Surgery (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			SNORE25 total, mean change from baseline (SD): -0.43 (0.56); P<0.001 -0.21 (0.56); P=0.06 Between groups difference (95% CI): -0.22 (-0.53 to 0.09); P=0.08 SF36 MCS, mean change from baseline (SD): 2.9 (7.3); P=0.08 0.4 (6.4); P=0.70 Between groups difference (95% CI): 2.5 (-1.4 to 6.4); P=0.10 SF36 PCS, mean change from baseline (SD): 0.5 (6.8); P=0.42 1.5 (7.8); P=0.44 Between groups difference (95% CI): -1.0 (-5.1 to 3.1); P=0.69	the Psychomotor Vigilance Task					

* (mean 7.2 months from final tx for G1 and mean 8.2 months from BL for G2)

Abbreviations: AHEAD=Action for Health in Diabetes; BL=baseline; CBV=cerebrovascular; CI=confidence interval; CV=cardiovascular; FOSQ=Functional Outcomes of Sleep Questionnaire; G=group; LAUP=laser assisted uvulopalatoplasty; MCS=Mental Component Score of the SF-36; MVA=motor vehicle accident; N=sample size; NR=not reported; PCS=Physical Component Score of the SF-36; RF=radiofrequency; SAQLI=Sleep Apnea Quality of Life Index; SD=standard deviation; SE=standard error; SF-36=36-Item Short Form Health Survey; VLCD=very low calorie diet.

Appendix E Table 19. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
Aarab, 2011[189]	MAD (20) Intraoral Placebo Device (19)	NR	SF-36 Mean (SD) Baseline: PF 82.98 (22.7) SF 75.0 (23.6) RF 53.9 (48.1) RE 77.2 (41.7) MH 66.7 (14.1) Vit 49.7 (18.0) BP 79.6 (27.9) GHP 54.7 (22.3) HT 41.3 (24.7) SF-36: Changes in the domains of SF-36 were not NS between groups at 24 weeks. Post-treatment values were NR.	NR	NR	NR	NR	NR	NR
Barnes, 2004[173]	MAD (99) Placebo (98)	0 (0.0) 0 (0.0)	FOSQ mean score, mean (SE): Baseline: 3.1 (0.1) 3.3 (0.1), p < 0.001 3.3 (0.1), p < 0.01 MAD vs. Placebo p < 0.05 FOSQ domains, mean (SE): General Productivity: Baseline: 3.2 (0.1) 3.4 (0.1), p < 0.001 3.4 (0.1), p < 0.01 MAD vs. Placebo p = NS Activity level: Baseline: 3.0 (0.1) 3.2 (0.1), p < 0.001 3.1 (0.1), p < 0.05 MAD vs. Placebo p = NS Sexual Relationships: Baseline: 2.9 (0.1) 3.0 (0.1), p = NS 3.0 (0.1), p = NS MAD vs. Placebo p = NS Social Outcomes: Baseline: 3.3 (0.1) 3.7 (0.1), p < 0.001	Reported: Word Pair Memory Recall; Logical Memory Test; Digit Span Backwards; Trailmaking B; Digit Symbol Substitution Task; COWAT; PVT; Stroop Color Association Test	NR	NR	NR	NR	NR

Appendix E Table 19. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			3.4 (0.1), p = NS MAD vs. Placebo p < 0.001 Vigilance: Baseline: 3.0 (0.1) 3.1 (0.1), p < 0.01 3.1 (0.1), p < 0.05 MAD vs. Placebo p = ns SF-36 mean score, mean (SE) Baseline: 69.4 (1.3) 73.7 (1.2); p <0.001 71.4 (1.4); P = NS MAD vs. placebo p = NS Overall health Baseline: 65.9 (1.7) 71.7 (1.6); p <0.001 68.7 (1.6); p = NS MAD vs. placebo p <0.05						
Bloch, 2000[214]	Total (24) MAD Monobloc first (8) MAD Herbst first (8) No treatment first (8)	0 (0.0) 0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Lam, 2007[180]	MAD (34) Usual care (33)	NR	SAQLI, mean (SEM) contd. Treatment-related symptoms Mean (SEM) 10 weeks 1.8 (0.2) SF36, mean (SEM); p-val of within group change from BL; between group change from BL vs. usual care Physical function baseline 84.7 (1.7) 82.3 (2.6) Physical function 10 weeks 86.5 (2.0); p=NS; p=NS 78.9 (3.6) General health baseline	NR	NR	NR	NR	NR	NR

Appendix E Table 19. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			50.8 (3.9) 51.2 (3.3) General health 10 weeks 58.1 (3.7); p<0.05; p=NS 54.8 (3) Mental health baseline 65.8 (2.9) 65.6 (2.5) Mental health 10 weeks 69.8 (3.1); p=NS; p=NS 68.0 (2.5)						
Petri, 2008[191]	MAD (33) Sham MAD (30) No tx (30)	0 (0.0) 0 (0.0) 1 (3.3)	SF-36 PCS, Mean (SD) Baseline: 45.5 (9.5) 48.1 (9.2) 46.6 (9.6) 4 weeks (within group p-value): 46.5 (8.0); P=0.21 47.5 (11.2); P=0.40 47.3 (8.7); P=0.69 SF-36 MCS, Mean (SD) Baseline: 47.2 (8.5) 48.8 (10.0) 50.2 (8.9) 4 weeks (within group p-value): 51.1 (8.0); P=0.039 49.8 (8.5); P=0.48 51.2 (7.8); P=0.79	NR	NR	NR	NR	NR	NR
Quinnell, 2014[197]	Total (90) No tx (22) SP1 - MAD (23) SP2 - MAD (22) bMAD (23)	0 0 0 0	FOSQ (p is change from no tx) Total Score 16.62 (2.55), no tx 17.13 (2.42), p < 0.05 17.70 (2.14), p < 0.05 17.90 (1.92), p < 0.05 General Productivity 3.48 (0.45), no tx 3.57 (0.44), p < 0.05 3.66 (0.40), p < 0.05 3.73 (0.36), p < 0.05	NR	2 (3%) 1 (1%) 0 (0%) 2 (3%)	**CV Events** 1 (1%) 0 (0%) 0 (0%) 1 (1%)	NR	NR	NR

Appendix E Table 19. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			Social Outcome 3.53 (0.58), no tx 3.61 (0.58) 3.71 (0.53), p < 0.05 3.74 (0.49), p < 0.05 Activity Level 3.11 (0.68), no tx 3.25 (0.59), p < 0.05 3.37 (0.53), p < 0.05 3.40 (0.48), p < 0.05 Vigilance 3.25 (0.57), no tx 3.33 (0.54) 3.48 (0.47), p < 0.05 3.53 (0.42), p < 0.05 Intimate Relationships 3.20 (0.87), no tx 3.34 (0.80) 3.45 (0.73), p < 0.05 3.49 (0.68), p < 0.05 SAQLI (p is change from no tx) Total Score 5.01 (1.24), no tx 5.25 (1.20), p<0.05 5.60 (1.12), p<0.05 5.64 (1.06), p<0.05 Daily Activities 4.83 (1.49), no tx 5.16 (1.38), p<0.05 5.56 (1.23), p<0.05 5.47 (1.33), p<0.05 Social Interactions 5.31 (1.25), no tx 5.49 (1.34) 5.85 (1.16), p<0.05 5.89 (1.12), p<0.05 Emotions 5.40 (1.25), no tx 5.46 (1.25) 5.70 (1.25), p<0.05 5.79 (1.09), p<0.05						

Appendix E Table 19. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
			Symptoms 4.47 (1.72), no tx 4.82 (1.59), p<0.05 5.23 (1.52), p<0.05 5.37 (1.47), p<0.05 SF36 (p is change from no tx) Physical component 43.06 (12.86), no tx 42.73 (12.22) 45.11 (12.33), p<0.05 43.12 (13.81) Mental component 46.20 (10.78), no tx 46.87 (9.63) 47.34 (11.24)						

Abbreviations: BL=baseline; bMAD=fully-bespoke mandibular advancement device; BP=bodily pain; CBV=cerebrovascular; COWAT=Controlled Oral Word Association Test; CV=cardiovascular; FOSQ=Functional Outcomes of Sleep Questionnaire; G=group; GHP=general health perceptions; HT=health transition; MAD=mandibular advancement device; MCS=Mental Component Score of the SF-36; MH=mental health; MVA=motor vehicle accident; N=sample size; NR=not reported; NS=not significant; PCS=Physical Component Score of the SF-36; PF=physical functioning; PVT=Psychomotor Vigilance Test; RE=role emotional; RP=role physical; SAQLI=Sleep Apnea Quality of Life Index; SD=standard deviation; SE=standard error; SF=social functioning; SF-36=36-Item Short Form Health Survey; SP=SleepPro; tx=treatment; Vit=vitality.

Appendix E Table 20. Characteristics of Included Prospective Cohort Studies for KQ 6

First Author, Year Cohort Name N	Study Groups (n)	Participants	Outcomes	Country	F/U	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI; ESS	% HTN	% DM	% Sm	Quality
Blackwell, 2015[290] MrOS Sleep[*] 2,636	AHI <15 (1,504) AHI ≥15 (1,132)	Community sample, men, ≥67 y/o	Cognitive decline	US	Mean 3.4 yr	76 (NR)	0	8.5	27	Median 12.4; NR	49	13	60[‡]	Fair
Ensrud, 2012[220] MrOS Sleep[*] 2,505	AHI ≥30 (209) AHI < 30 (2296)	Community based sample, men, ≥ 67 y/o	All-cause mortality	US	Mean 3.4 yr	76 (NR)	0	9.5	27	NR; NR[†]	NR	NR	60[‡]	Fair
Nieto, 2012[221] WSCS 1,522	AHI <5 (1157) AHI 5 to <15 (222) AHI 15 to <30 (84) AHI ≥30 (59)	community-based, random sample of employed adults, 30-60 y/o men and women	Cancer mortality; all-cause mortality	US	Up to 22 yr	48 (NR)	45	5	30	NR; NR	NR	NR	57[§]	Fair
Gooneratne, 2011[223] None 289	AHI ≥ 20 (66) AHI < 20 (223)	Community based sample, men and women > 65 y/o	All-cause mortality	US	Mean 13.8 yr	78 (NR)	74	26	26	14.5; NR	NR	NR	NR	Fair
Gottlieb, 2010[224] SHHS 4,422	AHI <5 (2434) AHI 5 to <15 (1254) AHI 15 to <30 (478) AHI ≥30 (256)	Community based sample, men and women ≥ 40 y/o	Incident CHD Incident HF	US	Med 8.7 yr	63 (NR)	56	22	28	2.7 to 6.2; NR	33[‖]	11	53[¶]	Good
Marin, 2005[50] 1,651	Untreated mild-moderate OSA (AHI 5-30) (403) Untreated severe OSA AHI >30 (235) Treated OSA with CPAP (372) Snorers (377) Healthy controls (264)	Community-based and sleep clinic, men with OSA or snoring	Fatal and non-fatal CV events	Spain	Mean 10.1 yr	50 (NR)	0	NR	26 to 31	NR; NR	15 to 35	6 to 11	23 to 25	Fair
Marshall, 2014[229] Marshall, 2008[228] Busselton Health Study 393	AHI < 5 (294) 5 ≤ AHI < 15 (81) AHI ≥ 15 (18)	Community-based sample, men and women, aged 40 to65	All-cause mortality	Australia	Up to 20 yrs	54 (NR)	26	NR	26 to 34	NR; NR	NR	3	16	Fair for all-cause mortality; poor for other outcomes

Appendix E Table 20. Characteristics of Included Prospective Cohort Studies for KQ 6

First Author, Year Cohort Name N	Study Groups (n)	Participants	Outcomes	Country	F/U	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI; ESS	% HTN	% DM	% Sm	Quality
Punjabi, 2009[227] SHHS 6,294	AHI <5 (3429) AHI 5-<15 (1797) AHI 15 to <30 (727) AHI ≥30 (341)	Community-based sample, ≥40 y/o, recruited from population-based studies of CV and pulmonary disease; not being treated for SDB	All-cause mortality; CAD-specific mortality	US	Mean 8.2 yr	63 (NR)	53	23	28	NR	52	11	54[#]	Good
Redline, 2010[225] SHHS 5,422	AHI <4.1 (1356) AHI 4.1-<9.5 (1355) AHI 9.5 to 19.1 (1356) AHI 19.1 to 164.5 (1355)	Community-based sample, ≥40 y/o	Stroke	US	Med 8.7 yr	Med 62-75 (NR)	55	22	28	6.9-19.2; NR	37[**]	12	55[††]	Good
Yaffe, 2011[222] Substudy of SOF 461 had PSG; 298 analyzed	AHI ≥15 (105) AHI < 15 (193)	Community based sample, women ≥ 65 y/o who had PSG in a substudy of SOF	Mild cognitive impairment; dementia	US	Mean 4.7 yr	82 (NR)	100	9.7	28	Median 10; NR	62	13	2	Fair
Young, 2008[226] WSCS 1,522	AHI <5 (1157) AHI 5 to <15 (220) AHI 15 to <30 (82) AHI ≥30 (63)	Community-based random sample of employed adults, 30-60 y/o men and women	All-cause mortality; CV mortality	US	Up to 18 yr; mean 13.8 yr	48 (NR)	45	5	28.6	NR;[1] NR[‡‡]	33	3	18	Good

[*] Outcomes of Sleep Disorders in Older Men (MrOS Sleep) study; they recruited from the Osteoporotic Fractures in Men (MrOS) Study
[†] 9% had AHI ≥30; 12% had ESS>10
[‡] 2% current and 57.7% past
[§] past = 38.6; current = 18.1
[‖] percentage on antihypertensive medications
[¶] 41% past and 12% current smokers
[#] 11% current, 43% former smokers
[**] percentage on antihypertensive medications
[††] 12% current and 43% former smokers
[‡‡] 25% had excessive daytime sleepiness

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; CAD=coronary artery disease; CHD=coronary heart disease; CV=cardiovascular; DM=diabetes mellitus; ESS=Epworth Sleepiness Scale; F=female; F/U=duration of followup; HF=heart failure; HTN=hypertension; Med=median; N=sample size; NR=not reported; PSG=polysomnography; SDB=sleep disordered breathing; SHHS=Sleep Heart Health Study; Sm=smokers; SOF=Study of Osteoporotic Fractures; US=United States; WSCS=Wisconsin Sleep Cohort Study; yr=years; y/o=years old.

Appendix E Table 21. Results of Included Prospective Cohort Studies Reporting Mortality by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	All-Cause Mortality, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Mortality, n Events, Adjusted HR/OR (95% CI)	Other Disease-Specific Mortality, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study that Were Not Included in the Final Model)
Ensrud, 2012[220] None Severe: ≥30 Not Severe: < 30	180 deaths Base Model OR 1.88 (1.15, 3.08) Multivariate model OR 1.74 (1.04, 2.89)	NR	NR	Base: age, race, clinic site, health status, and BMI Multivariate: age, race, site, health status, BMI, education, social support, alcohol intake, smoking, antidepressant, benzodiazepine, nonbenzodiazepine sedative hypnotic use, medical conditions, cognition, and baseline frailty status.
Gooneratne, 2011[223] None SDB+ (AHI ≥20)/EDS+ SBD-/EDS+ SDB+(AHI ≥20)/EDS-	160 deaths HR: SDB-/EDS- = Ref SDB+/EDS+ = 2.28 (1.46, 3.57) SBD-/EDS+ = 1.11 (0.75, 1.63) SDB+/EDS- = 0.74 (0.39, 1.38)	NR	NR	Final model included age, male gender, African American race, history of angina, habitual self-reported sleep duration > 8.5 h (other covariates considered: smoking, alcohol intake, BMI, habitual sleep parameters [self-reported sleep duration, sleep latency, sleep efficiency], polysomnography sleep parameters [sleep duration, sleep latency, wakefulness after sleep onset, sleep efficiency], oxyhemoglobin desaturation [nadir in REM and NREM sleep during polysomnography], and 22 medical conditions [diabetes, emphysema, high blood pressure, heart attack, stroke, heart failure, etc.]).
Marin, 2005[50] Untreated mild to mod: AHI 5-30 Untreated Severe: AHI >30 Treated OSA with CPAP: Any AHI >5 Snorers: AHI <5 Healthy controls: AHI <5	NR	81 fatal CV events (due to MI or stroke): 47 in untreated OSA participants; 13 in treated OSA group; 13 in simple snorers; and 8 in healthy men Partial adjusted OR Untreated mild to mod: 1.16 (0.55 to 2.11) Untreated severe: 3.02 (1.44 to 7.33) CPAP treated: 1.05 (0.45 to 2.09) Snorers: 1.03 (0.41 to 1.46) Fully adjusted OR Untreated mild to mod: 1.15 (0.34 to 2.69) Untreated severe: 2.87 (1.17 to	NR	Partial: Age, diagnostic group, diabetes, lipid disorders, smoking status, alcohol use, systolic and diastolic blood pressure, blood glucose, total cholesterol. Triglycerides, and current use of antihypertensive, lipid-lowering and antidiabetic drugs Full: above plus hypertension and presence of cardiovascular disease—i.e., ischemic heart disease, congestive heart disease, or cerebrovascular disease. Used matching for age and BMI

Appendix E Table 21. Results of Included Prospective Cohort Studies Reporting Mortality by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	All-Cause Mortality, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Mortality, n Events, Adjusted HR/OR (95% CI)	Other Disease-Specific Mortality, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study that Were Not Included in the Final Model)
		7.3) CPAP treated: 1.05 (0.39 to 2.21)Snorers: 1.03 (0.31 to 1.84)		
Marshall, 2008[228] Marshall, 2014[229] Busselton Health Study *For 14 year followup* RDI No OSA: 0 to 4 Mild: 5 to <15 Mod to severe: ≥15 *For 20 year followup:* Normal: < 5 Mild 5 to <15 Mod to severe: ≥15	*For 14 year followup:* 33 deaths (by group: 22, 5, and 6, respectively) Partially Adjusted HR No OSA: Ref Mild: 0.62 (0.23 to 1.69) Mod to severe: 4.40 (1.48 to 13.07), P=0.008 Fully Adjusted HR No OSA: Ref Mild: 0.47 (0.17 to 1.29) Mod to severe: 6.24 (2.01 to 19.39), P=0.002 *For 20 year followup:* 77 deaths G1: Ref G2: 0.51 (0.27 to 0.99) G3: 4.2 (1.9 to 9.2)	NR	NR	*For 14 year followup:* Partially adjusted for age, gender, BMI, smoking status, total cholesterol, HDL cholesterol, diabetes (yes/no), doctor diagnoses angina Fully adjusted: Everything in the partially adjusted model plus mean arterial pressure *For 20 year followup:* Adjusted for age, gender, body mass index (normal, overweight, obese), smoking status (never, ex, current), total cholesterol, high density lipoprotein cholesterol, mean arterial pressure, diabetes (yes/no), doctor-diagnosed angina (yes/no), and in mortality, stroke, and CHD models a history of cardiovascular disease (via record linkage yes/no).
Nieto, 2012[221] WSCS Normal: <5 Mild: 5 to <15: Mod: 15 to <30 Severe: ≥30	112 deaths HR: Normal: Ref Mild: 1.8 (1.1 to 2.8) Mod: 1.1 (0.5 to 2.5) Severe: 3.4 (1.7 to 6.7)		50 cancer-related deaths HR: Mild: 1.1 (0.5 to 2.7) Mod: 2.0 (0.7 to 5.5) Severe: 4.8 (1.7 to 13.2)	age, sex, BMI, smoking (analyses also with stratification for sleepiness and obesity; additional adjustment for alcohol use, physical activity, educational status, diabetes, waist circumference, and sleep duration did not materially change results [data NR]; analyses removing those treated with CPAP resulted in slightly increased HRs [data NR])

Appendix E Table 21. Results of Included Prospective Cohort Studies Reporting Mortality by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	All-Cause Mortality, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Mortality, n Events, Adjusted HR/OR (95% CI)	Other Disease-Specific Mortality, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study that Were Not Included in the Final Model)
Punjabi, 2009[227] SHHS No SDB: <5 Mild: 5-<15 Mod: 15 to <30 Severe: ≥30	1047 deaths Deaths by AHI: No SDB: 477 Mild: 319 Mod: 165 Severe: 86 All participants Adjusted HR: Model 1 No SDB: ref Mild: 0.90 (0.78 to 1.04) Mod: 1.16 (0.97 to 1.39) Severe: 1.30 (1.03 to 1.64) Adjusted HR: Model 2 No SDB: ref Mild: 0.93 (0.80 to 1.07) Mod: 1.20 (1.00 to 1.44) Severe: 1.38 (1.08 to 1.75) Adjusted HR: Model 3 No SDB: ref Mild: 0.93 (0.80 to 1.08) Mod: 1.17 (0.97 to 1.42) Severe: 1.46 (1.14 to 1.86) Men- all ages Adjusted HR: Model 1 No SDB: ref Mild: 0.94 (0.78 to 1.15) Mod: 1.23 (0.98 to 1.54) Severe: 1.30 (0.98 to 1.72) Adjusted HR: Model 2 No SDB: ref Mild: 0.99 (0.81 to 1.20) Mod: 1.30 (1.03 to 1.64) Severe: 1.42 (1.06 to 1.90)	CAD-specific mortality 220 deaths Limited data reported. In men, AHI ≥15 had a fully adjusted HR 1.69 (1.13 to 2.52). In women, an association was not identified between SDB and CAD-related deaths	NR	Sex was included in all models that used all participants Model 1: Age (continuous) and race Model 2: Age (continuous), race, BMI Model 3: Age (continuous), race, BMI, smoking status (current, never, former), systolic and diastolic blood pressure, prevalent hypertension, diabetes, and CV disease

Appendix E Table 21. Results of Included Prospective Cohort Studies Reporting Mortality by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	All-Cause Mortality, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Mortality, n Events, Adjusted HR/OR (95% CI)	Other Disease-Specific Mortality, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study that Were Not Included in the Final Model)
	Adjusted HR: Model 3 No SDB: ref Mild: 1.01 (0.83 to 1.24) Mod: 1.27 (1.00 to 1.65) Severe: 1.54 (1.15 to 2.08) Men- ≤70 yrs Adjusted HR: Model 1 No SDB: ref Mild: 1.10 (0.81 to 1.48) Mod: 1.37 (0.96 to 1.95) Severe: 1.67 (1.09 to 2.55) Adjusted HR: Model 2 No SDB: ref Mild: 1.16 (0.85 to 1.58) Mod: 1.44 (1.00 to 2.08) Severe: 1.88 (1.19 to 2.95) Adjusted HR: Model 3 No SDB: ref Mild: 1.24 (0.90 to 1.71) Mod: 1.45 (0.98 to 2.14) Severe: 2.09 (1.31 to 3.33) Men- >70 yrs Adjusted HR: Model 1 No SDB: ref Mild: 0.86 (0.67 to 1.11) Mod: 1.18 (0.87 to 1.58) Severe: 1.16 (0.80 to 1.69) Adjusted HR: Model 2 No SDB: ref Mild: 0.89 (0.69 to 1.16) Mod: 1.25 (0.92 to 1.70) Severe: 1.25 (0.85 to 1.83)			

Appendix E Table 21. Results of Included Prospective Cohort Studies Reporting Mortality by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	All-Cause Mortality, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Mortality, n Events, Adjusted HR/OR (95% CI)	Other Disease-Specific Mortality, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study that Were Not Included in the Final Model)
	Adjusted HR: Model 3 No SDB: ref Mild: 0.92 (0.70 to 1.20) Mod: 1.23 (0.90 to 1.68) Severe: 1.27 (0.86 to 1.86) Women – all ages Adjusted HR: Model 1 No SDB: ref Mild: 0.84 (0.68 to 1.04) Mod: 1.05 (0.77 to 1.42) Severe: 1.34 (0.86 to 2.07) Adjusted HR: Model 2 No SDB: ref Mild: 0.85 (0.68 to 1.06) Mod: 1.06 (0.78 to 1.43) Severe: 1.37 (0.88 to 2.13) Adjusted HR: Model 3 No SDB: ref Mild: 0.83 (0.66 to 1.04) Mod: 1.01 (0.73 to 1.38) Severe: 1.40 (0.89 to 2.22) Women- ≤70 yrs Adjusted HR: Model 1 No SDB: ref Mild: 1.00 (0.68 to 1.45) Mod: 1.11 (0.63 to 1.96) Severe: 1.73 (0.84 to 3.58) Adjusted HR: Model 2 No SDB: ref Mild: 0.99 (0.66 to 1.47) Mod: 1.12 (0.62 to 2.02) Severe: 1.75 (0.82 to 3.74)			

Appendix E Table 21. Results of Included Prospective Cohort Studies Reporting Mortality by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	All-Cause Mortality, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Mortality, n Events, Adjusted HR/OR (95% CI)	Other Disease-Specific Mortality, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study that Were Not Included in the Final Model)
	Adjusted HR: Model 3 No SDB: ref Mild: 0.97 (0.64 to 1.48) Mod: 1.15 (0.63 to 2.11) Severe: 1.76 (0.77 to 3.95) Women- >70 yrs Adjusted HR: Model 1 No SDB: ref Mild: 0.77 (0.60 to 1.00) Mod: 0.98 (0.68 to 1.40) Severe: 1.09 (0.62 to 1.89) Adjusted HR: Model 2 No SDB: ref Mild: 0.78 (0.60 to 1.02) Mod: 0.99 (0.69 to 1.42) Severe: 1.10 (0.63 to 1.92) Adjusted HR: Model 3 No SDB: ref Mild: 0.77 (0.58 to 1.00) Mod: 0.89 (0.61 to 1.31) Severe: 1.14 (0.65 to 2.01)			
Young, 2008[226] WSCS No SDB:<5 Mild: 5 to <15 Mod: 15 to <30 Severe: ≥30	80 deaths Adjusted HR: No SDB: ref Mild: 1.6 (0.9 to 2.8) Mod: 1.4 (0.6 to 3.3) Severe: 3.0 (1.4 to 6.3) Adjusted HR accounting for comorbidity: No SDB: ref Mild: 1.5 (0.8 to 2.8) Mod: 1.3 (0.5 to 3.2) Severe: 2.7 (1.3 to 5.7) Adjusted HR excluding those	25 deaths Adjusted HR: No SDB: ref Mild: 1.8 (0.7 to 4.9) Mod: 1.2 (0.3 to 5.8) Severe: 2.9 (0.8 to 10.0) Fully adjusted HR: Severe: 5.9 (2.6 to 13.3) Adjusted HR excluding those treated with CPAP (n=1396): No SDB: ref Mild: 1.3 (0.4 to 4.1) Mod: 1.5 (0.3 to 7.3)		Adjusted HRs: Age, age-squared, sex, BMI, BMI-squared Fully adjusted HR: Age, age-squared, sex, BMI, BMI-squared, smoking, alcohol use, general health status, educational status, neck girth, waist-hip ratio, sleep duration, and total cholesterol (authors did not consider this model robust for several reasons, including multicollinearity and potential model instability due to outliers and influential points which was of concern with a small number of outcomes; they just show this model to show that the adjusted HRs did not overestimate the HRs—if anything, they seem to underestimate them) Adjusted HRs also accounting for comorbidity: Age,

Appendix E Table 21. Results of Included Prospective Cohort Studies Reporting Mortality by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	All-Cause Mortality, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Mortality, n Events, Adjusted HR/OR (95% CI)	Other Disease-Specific Mortality, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study that Were Not Included in the Final Model)
	treated with CPAP (n=1396): No SDB: ref Mild: 1.4 (0.7 to 2.6) Mod: 1.7 (0.7 to 4.1) Severe: 3.8 (1.6 to 9.0)	Severe: 5.2 (1.4 to 19.2)		age-squared, sex, BMI, BMI-squared, hypertension/use of HTN meds, self-reported diabetes, coronary artery disease, cardiovascular disease, heart failure, myocardial infarction, cardiac surgery, and stroke

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; CAD=coronary artery disease; CI=confidence interval; CPAP=continuous positive airway pressure; CV=cardiovascular; EDS=excessive daytime sleepiness; HDL=high-density lipoprotein; HR=hazard ratio; HTN=hypertension; mod=moderate; MI=myocardial infarction; Mod=moderate; n=number; NR=not reported; NREM=non-rapid eye movement; OR=odds ratio; OSA=obstructive sleep apnea; RDI=respiratory disturbance index; Ref=reference; REM=rapid eye movement; SDB=sleep disordered breathing; SHHS=Sleep Heart Health Study; WSCS=Wisconsin Sleep Cohort Study.

Appendix E Table 22. Results of Included Prospective Cohort Studies Reporting Cardiovascular Events, Cerebrovascular Events, or Cognitive Impairment by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	Cardiovascular Events, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Events, n Events, Adjusted HR/OR (95% CI) Continued	Cognitive Impairment, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study That Were Not Included in The Final Model)
Blackwell, 2015[290] MrOS Sleep Normal or mild: < 15 Mod to severe: ≥ 15	NR	NR	Trails B: Normal to mild: Ref Mod to severe: 1.14 (0.84 to 1.54) Modified Mini-Mental State Examination (3MS) Normal to mild: Ref Mod to severe: 0.99 (0.79 to 1.24)	Age, site, race, BMI, education, number of depressive symptoms, history of diabetes, history or stroke or transient ischemic attack, history of hypertension, history of CHD, history of Parkinson's disease, impairment in instrumental activities of daily living, benzodiazepine use, antidepressant use, self-reported health status, physical activity, alcohol use, and smoking status.
Gottlieb, 2010[224] SHHS Normal: <5 Mild: 5 to <15 Mod: 15 to <30 Severe: ≥30	**Incident CHD events, n** Total: 473 (76 CHD deaths, 186 MIs, 212 coronary revascularization procedures) Men: 296 Women: 177 **Incident CHD, men, HR** Normal: Ref 1. Mild: 0.94 (0.71 to 1.24) Mod: 1.07 (0.75 to 1.52) Severe: 1.45 (0.99 to 2.13) 2. Mild: 0.93 (0.70 to 1.23) Mod: 1.04 (0.73 to 1.48) Severe: 1.41 (0.96 to 2.07) 3. Mild: 0.91 (0.69 to 1.20) Mod: 1.07 (0.75 to 1.52) Severe: 1.33 (0.91 to 1.95)	**Incident HF events, n** Total: 308 Men: 141 Women: 167 **Incident HF, men, HR** Normal: Ref 1. Mild: 0.96 (0.63 to 1.46) Mod: 1.17 (0.71 to 1.94) Severe: 1.61 (0.95 to 2.71) 2. Mild: 0.90 (0.59 to 1.38) Mod: 1.08 (0.65 to 1.80) Severe: 1.59 (0.94 to 2.69) 3. Mild: 0.88 (0.57 to 1.35) Mod: 1.13 (0.68 to 1.89) Severe: 1.58 (0.93 to 2.66) **Incident HF, women, HR** 1. Mild: 1.12 (0.79 to 1.59) Mod: 1.10 (0.66 to 1.83) Severe: 1.05 (0.50 to 2.23) 2. Mild: 1.15 (0.81 to 1.63) Mod: 1.06 (0.64 to 1.77) Severe: 1.19 (0.56 to 2.53) 3. Mild: 1.13 (0.80 to 1.61) Mod: 1.01 (0.60 to 1.69) Severe: 1.19 (0.56 to 2.52)		Model 1. age, race, BMI, smoking Model 2. age, race, BMI, smoking, total and HDL cholesterol, lipid-lowering medications, diabetes mellitus Model 3. age, race, BMI, smoking, total and HDL cholesterol, lipid-lowering medications, diabetes mellitus, SBP, DBP, use of antihypertensive medications

Appendix E Table 22. Results of Included Prospective Cohort Studies Reporting Cardiovascular Events, Cerebrovascular Events, or Cognitive Impairment by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	Cardiovascular Events, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Events, n Events, Adjusted HR/OR (95% CI) Continued	Cognitive Impairment, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study That Were Not Included in The Final Model)
	Incident CHD, women, HR 1. Mild: 1.01 (0.73 to 1.45) Mod: 0.92 (0.54 to 1.55) Severe: 0.36 (0.11 to 1.16) 2. Mild: 0.99 (0.71 to 1.40) Mod: 0.89 (0.52 to 1.51) Severe: 0.37 (0.12 to 1.19) 3. Mild: 0.98 (0.69 to 1.38) Mod: 0.87 (0.51 to 1.49) Severe: 0.40 (0.12 to 1.27)			
Marin, 2005[50] Untreated mild to mod: AHI 5-30 Untreated Severe: AHI >30 Treated OSA with CPAP: Any AHI >5 Snorers: AHI <5 Healthy controls: AHI <5	144 Non-fatal cardiovascular events (non-fatal MI, non-fatal stroke, coronary bypass surgery, percutaneous transluminal coronary angiography): 86 in untreated OSA participants; 24 in treated OSA group; 22 in simple snorers; and 12 in healthy men Partial adjusted OR Untreated mild to mod: 1.62 (0.65 to 3.01) Untreated severe: 3.32 (1.24 to 7.41) CPAP treated: 1.42 (0.53 to 3.29) Snorers: 1.23 (0.71 to 2.86)	NR	NR	Partial: Age, diagnostic group, diabetes, lipid disorders, smoking status, alcohol use, systolic and diastolic blood pressure, blood glucose, total cholesterol. Triglycerides, and current use of antihypertensive, lipid-lowering and antidiabetic drugs Full: above plus hypertension and presence of cardiovascular disease—i.e., ischemic heart disease, congestive heart disease, or cerebrovascular disease. Used matching for age and BMI

Appendix E Table 22. Results of Included Prospective Cohort Studies Reporting Cardiovascular Events, Cerebrovascular Events, or Cognitive Impairment by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	Cardiovascular Events, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Events, n Events, Adjusted HR/OR (95% CI) Continued	Cognitive Impairment, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study That Were Not Included in The Final Model)
	Fully adjusted OR Untreated mild to mod: 1.57 (0.62 to 3.16) Untreated severe: 3.17 (1.12 to 7.52) CPAP treated: 1.42 (0.52 to 3.40) Snorers: 1.32 (0.64 to 3.01)			
Redline, 2010[225] SHHS Men Quartile I: <4.1 Quartile II: 4.1-<9.5 Quartile III: 9.5 to 19.1 Quartile IV: 19.1 to 164.5		Incident ischemic stroke 193 total (15 fatal), 85 in men and 108 in women **Age Adjusted HR** **Men** AHI <4.1: ref AHI 4.1-<9.5: 1.86 (0.68 to 5.13) AHI 9.5 to 19.1: 1.97 (0.74 to 5.21) AHI 19.1 to 164.5: 3.05 (1.21 to 7.72) **Women** AHI <4.1: ref AHI 4.1-<9.5: 1.34 (0.77 to 2.34) AHI 9.5 to 19.1: 1.26 (0.72 to 2.20) AHI 19.1 to 164.5: 1.24 (0.69 to 2.22) **Fully Adjusted HR** **Men** AHI <4.1: ref AHI 4.1-<9.5: 1.86 (0.67 to 5.12) AHI 9.5 to 19.1: 1.86 (0.70 to 4.95) AHI 19.1 to 164.5: 2.86 (1.10 to 7.39) **Women** AHI <4.1: ref AHI 4.1-<9.5: 1.34 (0.76 to 2.36) AHI 9.5 to 19.1: 1.20 (0.67 to		Fully adjusted model included age, BMI, smoking status, SBP, use of antihypertensive medications, diabetes status, and race (secondary analyses addressed atrial fibrillation also; including it did not materially change the findings)

Appendix E Table 22. Results of Included Prospective Cohort Studies Reporting Cardiovascular Events, Cerebrovascular Events, or Cognitive Impairment by AHI (KQ 6)

First Author, Year Study Name AHI Cutpoints	Cardiovascular Events, n Events, Adjusted HR/OR (95% CI)	Cardiovascular Events, n Events, Adjusted HR/OR (95% CI) Continued	Cognitive Impairment, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study That Were Not Included in The Final Model)
		2.16) AHI 19.1 to 164.5: 1.21 (0.65 to 2.24)		
Yaffe, 2011[222] SOF SDB+: ≥ 15 SDB-: < 15			Mild cognitive impairment or dementia* Unadjusted OR 1.80 (1.10, 2.93) Adjusted OR 1.85 (1.11, 3.08) Additional adjustment OR 2.36 (1.34, 4.13)	Adjusted: age, race, body mass index, education level, smoking status, presence of diabetes, presence of hypertension, antidepressant use, benzodiazepine use, and use of nonbenzodiazepine anxiolytics. Additional adjustment models also adjusted for baseline cognitive test scores.

* Shortened mini-mental state exam and modified Trails B at baseline. Followup included: Trails B, modified mini-mental state examination, California Verbal Learning Test, Digit Span, and category and verbal fluency tests.

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; CHD=cardiovascular heart disease; CI=confidence interval; CPAP=continuous positive airway pressure; DBP=diastolic blood pressure; HDL=high-density lipoprotein; HF=heart failure; HR=hazard ratio; mod=moderate; MI=myocardial infarction; NA=not applicable; NR=not reported; OR=odds ratio; OSA=obstructive sleep apnea; RDI=respiratory disturbance index; Ref=reference; SDB=Sleep Disordered Breathing; SBP=systolic blood pressure; SHHS=Sleep Heart Health Study; SOF=Study of Osteoporotic Fractures; WSCS=Wisconsin Sleep Cohort Study.

Appendix E Table 23. Results of Included Randomized, Controlled Trials: Harms of CPAP Compared With Sham or Control (KQ 8)

First Author, Year Trial Name Quality for Harms	G1 (N) G2 (N)	DC Due to Harms, N (%)	Rash, N (%)	Irritation, N (%)	Need for Additional Sleep Meds, N (%)	Claustrophobia, N (%)	Oral or Nasal Dryness, N (%)	Nosebleed, N (%)	Pain, N (%)	Excess Salivation, N (%)	Dental, N (%)
Engleman, 1999[176] Fair	Total (37) CPAP first (NR) Oral Placebo first (NR)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	4 (12) 0 (0)	NR	0 (0.0) 1 (2.9)	NR	NR
Hui, 2006[141] Fair	CPAP (28) Sham CPAP (28)	0 (0.0) 5 (17.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kushida, 2012[145] APPLES Fair	CPAP (556) Sham CPAP (542)	NR	Dermato-logical 102 (18.3) 61 (11.3)	NR	NR	NR	NR	NR	NR	NR	NR
Lam, 2007[180] Fair	CPAP (34) Usual care (33)	0 (0.0) 0 (0.0)	NR	Facial skin abrasion: 7 (21) 0 (0)	NR	NR	16 (47) 0 (0)	NR	TMJ pain: 0 (0.0) 0 (0.0)	0 (0) 0 (0)	0 (0) 0 (0)
Malow, 2008[150] Fair	Total (35) CPAP (22) Sham CPAP (13)	0 (0.0) 0 (0.0)	NR	2 (9.1) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Redline, 1998[183] Fair	CPAP (59) Conservative therapy (52)	3 (5.1) 0 (0.0)	NR	2 (3.3) 0 (0.0)	NR	NR	NR	1 (1.7) 2 (3.6)	NR	NR	NR
Smith, 2007[163] Fair	Total (24) CPAP first (11) Sham first (13)	0 (0.0) 1 (3.9)	NR	NR	NR	1 (3.9) but unclear which arm	NR	NR	NR	NR	NR
Weaver, 2012[166] Fair	CPAP (141) Sham CPAP (140)	1 (0.8) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR

Appendix E Table 23. Results of Included Randomized, Controlled Trials: Harms of CPAP Compared With Sham or Control (KQ 8)

First Author, Year Trial Name Quality for Harms	G1 (N) G2 (N)	DC Due to Harms, N (%)	Rash, N (%)	Irritation, N (%)	Need for Additional Sleep Meds, N (%)	Claustrophobia, N (%)	Oral or Nasal Dryness, N (%)	Nosebleed, N (%)	Pain, N (%)	Excess Salivation, N (%)	Dental, N (%)
Weinstock, 2012[167,289] Fair	Total (50) CPAP first (25) Sham CPAP first (25)	0 (0.0) 0 (0.0)	NR	Skin irritation: 6 (12.0) 2 (4.0) Eye irritation: 1 (2.0) 0 (0.0)	NR	0 (0.0) 1 (2.0)	NR	NR	Ear pain: 1 (2.0) 0 (0.0) Non-cardiac chest pain: 1 (2.0) 0 (0.0)	NR	NR

Abbreviations: addl=additional; APPLES=Apnea Positive Pressure Long-term Efficacy Study; claustro=claustrophobia; CPAP=continuous positive airway pressure; DC=discontinued; G=group; MAD=mandibular advancement device; meds=medications; N=sample size; NR=not reported; saliv=salivation; TMJ=temporomandibular; UC=usual care; wks=weeks.

Appendix E Table 24. Results of Included Randomized, Controlled Trials: Harms of MADs Compared With Sham or Control (KQ 8)

First Author, Year Trial Name	G1 (N) G2 (N)	DC Due to Harms, N (%)	Rash, N (%)	Irritation, N (%)	Need for Addl Sleep Meds, N (%)	Claustro, N (%)	Oral or Nasal Dryness, N (%)	Nosebleed, N (%)	Excess Saliv, N (%)	Pain, N (%)	Dental, N (%)
Aarab, 2011[189]	MAD (20) Intraoral Placebo Device (19)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	4 (20.0) 0 (0.0)	NR	9 (45.0) 0 (0.0)	10* (50.0) 0 (0.0)	9† (45.0) 0 (0.0)
Bloch, 2000[214]	Total (24) MAD Monobloc first (8) MAD Herbst first (8) No treatment first (8)	0 (0.0) 0 (0.0)	NR	NR (but reported dental discomfort and mucosal erosions—see Dental column)	NR	NR	NR	NR	NR	TMJ pain Both MADs: 7 (29.2) No tx: 0 (0.0) Muscle discomfort Both MADs: 4 (16.7) No tx (0.0)	Dental discomfort Both MADs: 3 (12.5) No tx: 0 (0.0) Mucosal erosions Herbst MAD: 3 (12.5) Monobloc MAD: 0 (0.0) No tx: 0 (0.0)
Durán-Cantolla, 2015[36]	Total (42) MAD first (NR) Sham MAD first (NR)	NR	NR	NR	NR	NR	Oral dryness: 2 (4.8) 1 (2.6)	NR	15 (35.7) 22 (57.9)	Dental or gingival pain: 7 (16.7) 4 (10.5) Tongue pain: 3 (7.1) 4 (10.5) TMJ pain: 3 (7.1) 1 (2.6)	Temporal bite change: 5 (11.9) 2 (5.3) Damage to dental restorations: 2 (5.1) 1 (2.6)
Johnston, 2002[195]	Total (21) MAD first (13) Sham first (8)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR (68)	TMJ discomfort on waking: NR (42) NR Persistent TMJ discomfort: 1 (5.0) NR	Temporary occlusal changes: NR (4)

Appendix E Table 24. Results of Included Randomized, Controlled Trials: Harms of MADs Compared With Sham or Control (KQ 8)

First Author, Year Trial Name	G1 (N) G2 (N)	DC Due to Harms, N (%)	Rash, N (%)	Irritation, N (%)	Need for Addl Sleep Meds, N (%)	Claustro, N (%)	Oral or Nasal Dryness, N (%)	Nosebleed, N (%)	Excess Saliv, N (%)	Pain, N (%)	Dental, N (%)
Lam, 2007[180]	MAD (34) Usual care (33)	4 (11.8) 0 (0.0)	NR	NR	NR	NR	11 (33) 0 (0)	NR	19 (56) 0 (0)	TMJ pain: 13 (38) 0 (0.0)	11 (33) 0 (0)
Naismith, 2005[192] Gotsopoulos, 2002[193] Gotsopoulos, 2004[194]	Total (67) MAD first (35) Sham MAD first (32)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR; P<0.05	Jaw discomfort: NR; P<0.0001	Tooth tenderness: NR; P<0.0001
Petri, 2008[191]	MAD (33) Sham MAD (30) No tx (30)	4 (12.1) 2 (6.7) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR	1 (3.0) 0 (0.0) 0 (0.0)	1 (3.0) 1 (3.3) 0 (0.0)
Quinnell, 2014[197]	Total (90) SP1 - MAD (23) SP2 - MAD (22) bMAD (23) No tx (22)	1 (4.3) 0 (0) 2 (8.6) 0 (0)	NR	NR	NR	NR	20 (24.7) 24 (30.8) 18 (23.4) 10 (12.8)	NR	32 (39.5) 18 (23.1) 29 (37.7) 2 (2.6)	60‡ (74.1) 52 (66.7) 74 (96.1) 13 (16.7)	1 (4.3) 0 (0) 2 (8.6) 0 (0)

* Discomfort in wearing MAD
† Data reported were for sensitive teeth upon awakening (Study also reported tenderness in the masseter muscle region upon awakening, n=13 in MAD group)
‡ Data were for "discomfort/mouth problems"

Abbreviations: addl=additional; bMAD=fully-bespoke mandibular advancement device; claustro=claustrophobia; DC=discontinuation; G=group; meds=medications; MAD=mandibular advancement device; N=sample size; NR=not reported; saliv=salivation; SP=SleepPro; TMJ=temporomandibular; tx=treatment.

Table E25. Results of Included Randomized, Controlled Trials: Harms of Weight Loss Interventions Compared With Sham or Control (KQ 8)

First Author, Year Trial Name Quality for Harms	G1 (N) G2 (N)	DC Due to Harms, N (%)	Rash, N (%)	Irritation, N (%)	Need for Addl Sleep Meds, N (%)	Claustro, N (%)	Oral or Nasal Dryness, N (%)	Nosebleed, N (%)	Pain, N (%)	Excess Saliv, N (%)	Dental, N (%)
Johansson, 2009[207] Fair	Weight loss (30) Usual care (33)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	Dry lips: 1 (3.3) 0 (0.0)	NR	NR	NR	NR

Abbreviations: addl=additional; claustro=claustrophobic; DC=discontinued: G=group; N=number; NR=not reported; saliv=salivation.

Appendix E Table 26. Results of Included Randomized, Controlled Trials: Harms of Surgical Treatment (KQ 8)

First Author, Year Trial Name	G1 (N) G2 (N)	Periop Death, N (%)	Pain N(%)	Hemrg, N (%)	Nerve Palsy, N (%)	Addl Emerg Surgery, N (%)	CV Events, N (%)	Resp Failure, N (%)	Rehosp, N (%)	Speech or Voice Changes, N (%)	Diff Swallow, N (%)	Airway Stenosis, N (%)	Other
Bäck, 2009[198] Fair	Soft palate RF surgery (17) Sham surgery (15)	0 (0.0) 0 (0.0)	Data in figure only, VAS, p<0.05 on POD #1	NR	NR	NR	NR	NR	NR	Greater difficulty for G1 than G2 after 1 day (P<0.05); values reported in figure only	NR	NR	Swelling sensation: Data in figure only, VAS, p<0.05 on POD #1, 2, 3, 4, and 6 Drinking: Data in figure only, VAS, NS Breathing: Data in figure only, VAS, NS Opening the mouth: Data in figure only, VAS, NS
Browaldh, 2013[199] SKUP3 Fair	UPPP (33) No treatment (34)	0 (0.0) NA	4 (13) NA	Post-operative bleeding: 2 (6) NA	NR	NR	NR	NR	NR	NR	NR	NR	
Dixon, 2012[200] Fair	Bariatric Surgery (30) Conven-tional Weight loss program (30)	0 (0.0) NA	NR	NR	NR	NR	NR	NR	1 (3.3) NA	NR	NR	NR	One patient in the surgery group experienced an acute proximal gastric pouch dilation causing obstructive symptoms and requiring elective laporascopic replacement of the LAGB at 1 month.

Appendix E Table 26. Results of Included Randomized, Controlled Trials: Harms of Surgical Treatment (KQ 8)

First Author, Year Trial Name	G1 (N) G2 (N)	Periop Death, N (%)	Pain N(%)	Hemrg, N (%)	Nerve Palsy, N (%)	Addl Emerg Surgery, N (%)	CV Events, N (%)	Resp Failure, N (%)	Rehosp, N (%)	Speech or Voice Changes, N (%)	Diff Swallow, N (%)	Airway Stenosis, N (%)	Other
Woodson, 2003[203] Fair	TCRFTA surgery (30) Sham surgery (30)	0 (0.0) 0 (0.0)	10-cm VAS pain scale (SD): 1 week 1.64 (2.19) 1.84 (2.35) 3 weeks 0.71 (1.13) 0.33 (0.65)	NR	NR	NR	NR	NR	NR	NR	10-cm VAS swallowing scale (SD): 1 week 2.14 (2.52) 1.73 (2.44) 3 weeks 0.85 (1.36) 0.57 (0.99)	NR	Hematomas: 3 (12) 3 (11) Ulcerations: 1 (4) 0 (0) Infections: 0 (0) 0 (0)
Ferguson, 2002[201] Fair	LAUP (21) No treatment (25)	0 (0) NA	17 (81) NA	4 (19) mild bleeding; 5 (24) mod to severe bleeding NA	NR	NR	NR	NR	NR	1 (5) change in vocal quality NA	4 (19) NA	NR	Temporary nasal regurgitation: 5 (24) Mild infection: 4 (19) NA

Abbreviations: addl=additional; CV=cardiovascular; CI=confidence interval; DC=discontinued; diff swallow=difficulty swallowing; emerg=emergency; G=group; hemrg=hemorrhage; LAGB=laparoscopic adjustable gastric banding; LAUP=laser assisted uvulopalatoplasty; MVA=motor vehicle accident; N=sample size; NA=not applicable; NR=not reported; OR=odds ratio; periop=perioperative; POD=postoperative day; rehosp=rehospitalization; RF=radiofrequency; resp=respiratory; SD=standard deviation; TCRFTA=temperature-controlled radiofrequency tissue ablation; UC=usual care; UPPP=uvulopalatopharyngoplasty; VAS =visual analog scale; wks=weeks.

Appendix E Table 27. Characteristics of Studies Excluded From KQ 2 Because of Poor Quality

First Author, Year Country Study design	N	Participants	Questionnaire(s)/ Tool(s) Name	Questionnaire(s)/ Tool(s) Components	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	% HTN; % HF	% With OSA
Chung, 2008[69] Canada Cross-sectional	2467 completed STOP; 211 had PSG (34 in pilot and 177 in validation sample*)	Preoperative clinics	STOP and STOP-BANG	STOP Questionnaire - snoring, tiredness during the daytime, observed apnea, high blood pressure STOP-Bang – STOP plus BMI, Age, neck circumference, gender	55 (NR)	50	NR	30	20	41 NR	Any: 69 Mild: 29 Mod: 18 Severe: 22
Gurubhagavatula, 2004[105] United States Cross-sectional	1329; 406 had PSG†	Random sample of commercial driver's license holders within 50 miles of their sleep center in PA	Single stage models used the MVAP score; Two stage models used MVAP plus ODI from PM for those with intermediate MVAP scores	MVAP combined symptoms of snoring, choking, and witnessed apneas with BMI, age, and sex	44 (NR)	7	15	28	NR	NR	Weighted average sample: No OSA: 72 At least mild: 28 At least mod: 11 Severe:5

* Population characteristics entered in this table are for the validation sample

† Sample who had PSG was enriched for the presence of OSA by inviting those with the highest risk (based on MVAP) and then randomly sampling a smaller number from the lower risk participants. About 45% (247/551) of the higher-risk stratum and 20% (159/778) of the lower-risk stratum ultimately underwent PSG

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; F=female; HF=heart failure; HTN=hypertension; Mod=moderate; MVAP=multivariable apnea prediction; N=sample size; NR=not reported; ODI=oxygen desaturation index; OSA=obstructive sleep apnea; PA=Pennsylvania; PM=portable monitor; PSG=polysomnography; STOP=snoring, tiredness, observed apnea, high blood pressure.

Appendix E Table 28. Results of Studies Excluded Because of Poor Quality: Accuracy of Screening Questionnaires and Clinical Prediction Tools (KQ 2)

First Author, Year	Questionnaire/Tool Name Cutoff Value	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Calibration*	Others
Chung, 2008[69]	STOP Questionnaire to predict AHI > 5 STOP high risk (yes to 2 or more) vs. low risk	65.6 (56.4 to 73.9)	60.0 (45.9 to 73.0)	0.703	NR	PPV 78.4 (69.2 to 86.0) NPV 44.0 (32.6 to 56.0)
Chung, 2008[69]	STOP Questionnaire to predict AHI > 15 STOP high risk (yes to 2 or more) vs. low risk	74.3 (62.4 to 84.0)	53.3 (43.4 to 63.0)	0.722	NR	PPV 51.0 (41.3 to 60.7) NPV 76.0 (64.8 to 85.1)
Chung, 2008[69]	STOP Questionnaire to predict AHI > 30 STOP high risk (yes to 2 or more) vs. low risk	79.5 (63.5 to 90.7)	48.6 (40.0 to 63.0)	0.769	NR	PPV 30.4 (21.7 to 40.3) NPV 89.3 (80.1 to 95.3)
Chung, 2008[69]	STOP-BANG to predict AHI > 5 STOP-BANG high risk (yes to ≥3) vs. low risk	83.6 (75.8 to 89.7)	56.4 (42.3 to 69.7)	0.806	NR	PPV 81.0 (73.0 to 87.4) NPV 60.8 (46.1 to 74.2)
Chung, 2008[69]	STOP-BANG to predict AHI > 15 STOP-BANG high risk (yes to ≥3) vs. low risk	92.9 (84.1 to 97.6)	43.0 (33.5 to 52.9)	0.782	NR	PPV 51.6 (42.5 to 60.6) NPV 90.2 (78.6 to 96.7)
Chung, 2008[69]	STOP-BANG to predict AHI > 30 STOP-BANG high risk (yes to ≥3) vs. low risk	100 (91.0 to 100.0)	37.0 (28.9 to 45.6)	0.822	NR	PPV 31.0 (23.0 to 39.8) NPV 100 (93.0 to 100.0)
Gurubhaga-vatula, 2004[105]	MVAP to predict severe OSA (AHI ≥ 30) 0.55	0.808 (0.516 to 0.905)	0.728 (0.719 to 0.802)	0.841 (0.707 to 0.872)	NR	LR Neg 0.264 (0.123 to 0.568)

Appendix E Table 29. Results of Studies Excluded Because of Poor Quality: Accuracy of Screening Questionnaires and Clinical Prediction Tools (KQ 2)

First Author, Year	Questionnaire/Tool Name Cutoff value	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Calibration*	Others
Gurubhagavatula, 2004[105]	MVAP to predict any OSA (AHI ≥ 5) 0.5	0.724 (0.655 to 0.792)	0.756 (0.651 to 0.764)	0.798 (0.737 to 0.823)	NR	LR Neg 0.365 (0.289 to 0.495)
Gurubhagavatula, 2004[105]	Two-stage model: MVAP+PM to predict severe OSA (AHI ≥ 30) 0.9, 0.3, 10[a]	0.909 (0.719 to 0.969)	0.906 (0.845 to 0.910)	0.937 (0.936 to 0.939)	NR	LR Neg 0.100 (0.035 to 0.323)
Gurubhagavatula, 2004[105]	Two-stage model: MVAP+PM to predict any OSA (AHI ≥ 5) 0.9, 0.2, 5[a]	0.744 (0.609 to 0.765)	0.892 (0.869 to 0.937)	0.881 (0.869 to 0.887)	NR	LR Neg 0.287 (0.257 to 0.432)

* Upper bound for MVAP, lower bound for MVAP, and ODI threshold

Abbreviations: AHI=apnea-hypopnea index; AUROC=area under the receiver operating characteristic curve; CI=confidence interval; LR=likelihood ratio; MVAP=multivariate apnea prediction; Neg=negative; NPV=negative predictive value; NR=not reported; ODI=oxygen desaturation index; OSA=obstructive sleep apnea; PM=portable monitor; PPV=positive predictive value; STOP=snoring, tiredness, observed apnea, high blood pressure.

Appendix E Table 30. Characteristics of Randomized, Controlled Trials of Mandibular Advancement Devices Excluded Because of Poor Quality

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, wks	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF
Blanco, 2005[294] Parallel	MAD (12) Sham (12)	NR	No	Spain	12	53-56	17	NR	28	24-34	15-16	Mild to severe	NR; 0%
Mehta, 2001[295] Cross-over	Total (28) MAD first (NR) Sham MAD first (NR)	Sleep clinic	No	Australia	1-2*	48 (35-73)	21	NR	29	27	NR	Mild to severe	NR NR

* 3 weeks total; ABB/BAA design, so some patients were on MAD for 1 week and others for 2 weeks

Abbreviations: AHI=apnea hypopnea index; BMI=body mass index; Dur=duration; ESS=Epworth Sleepiness Scale; F=female; G=group; HF=heart failure; HTN=hypertension; MAD=mandibular advancement device; N=sample size; NR=not reported; OSA=obstructive sleep apnea; pts=patients; wks=weeks.

Appendix E Table 31. Results of Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices and Reported Health Outcomes That Were Excluded Because of Poor Quality (KQ 5)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment[f]	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)
Blanco, 2005[294]	MAD (12) Sham (12)	0 (0.0) 0 (0.0)	FOSQ (total score), mean (SD) Baseline 78.1 (22.6) 83.7 (20.8) 12 weeks 99.3 (14.4), p < 0.05 82.3 (13.9), p = NS SF-36, mean (SD) Physical function Baseline 70.7 (16.4) 71.5 (20.7) 12 weeks 74.1 (18.4), p = NS 78.8 (19.1), p = NS Mental health Baseline 60.1 (19.3) 52 (15.7) 12 weeks 59.4 (19.2), p = NS 56.0 (18.0), p = NS General health Baseline 60.7 (22.0) 57.4 (6.8) 12 weeks 61.0 (20.7), p = NS 58.4 (10.5), p = NS	NR	NR	NR	NR	NR	NR
Mehta, 2001[295] Cross-over	Total (28) MAD first (NR) Sham MAD first (NR)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CBV=cerebrovascular; CV=cardiovascular; FOSQ=Functional Outcomes of Sleep Questionnaire; G=group; MAD=mandibular advancement device; MVA=motor vehicle accident; N=number; NR=not reported; NS=not significant; SD=standard deviation; SF-36=36-Item Short Form Health Survey.

Appendix E Table 32. Characteristics of Prospective Cohort Studies Excluded From KQ 6 Because of Poor Quality

First Author, Year Cohort Name N	Study Groups (n)	Participants	Outcomes	Country	F/U	Mean (Range) Age	% F	% Non-White	Mean BMI	Mean AHI; ESS	% HTN	% DM	% Sm
Arzt, 2005[230] WSCS 1,475 (1,189 in longitudinal analysis)	AHI <5 (1,121) AHI 5 to <20 (255) AHI ≥20 (99)	Community-based, random sample of employed adults, 30-60 y/o men and women	Stroke	US	Up to 12 yr	47 (NR)	45	5	30	NR; NR	32	3	18
Munoz, 2006[231] Vitoria Sleep Project 394	AHI <30, No OSA to mod (299) AHI ≥30, severe (95)	Community-based sample, aged 70 to 100, noninstitutionalized	Ischemic stroke	Spain	Up to 6 yr; mean 4.5 yr	77 (NR)	43	NR	29	20 to 28;* NR	67	16	12
Saint Martin, 2015[232] 559	AHI <15 (156) 15 ≤ AHI ≤ 30 (304) AHI >30 (99)	Community sample, men and women, 65 yrs old at intake	Cognitive function	France	8 yrs	67	60	NR	24.9	21.0; 5.8	42.3	3.8	NR

* Reported mean AHI for those without incident stroke (20.1) and those with incident stroke (28).

Abbreviations: AHI=apnea hypopnea index; BMI=body mass index; DM=diabetes mellitus; ESS=Epworth Sleepiness Scale; F=female; F/U=followup; HTN=hypertension; N=number; NR=not reported; OSA=obstructive sleep apnea; Sm=smokers; US=United States; WSCS=Wisconsin Sleep Cohort Study; y/o=years old; yr=year.

Appendix E Table 33. Results of Prospective Cohort Studies Excluded From KQ 6 Because of Poor Quality That Reported Cardiovascular Events, Cerebrovascular Events, or Cognitive Impairment by AHI

First Author, Year Study Name AHI Cutpoints	Cardiovascular Events, n Events, Adjusted HR/OR (95% CI)	Cerebrovascular Events, n Events, Adjusted HR/OR (95% CI)	Cognitive Impairment, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study That Were Not Included in the Final Model)
Arzt, 2005[230] WSCS No SDB: <5: Mild: 5 to <20 Mod to severe: ≥20	NR	14 participants had a first-ever stroke (9, 1, and 4, respectively) Adjusted OR for Incidence of stroke: Model 2B No SDB: ref Mild:0.35 (0.05 to 2.69) Mod to severe: 4.48 (1.31 to 15.33) Model 3B No SDB: ref Mild:0.29 (0.04 to 2.36) Mod to severe: 3.08 (0.74 to 12.81)	NR	Model 2B: age, sex Model 3B: age, sex, BMI
Munoz, 2006[231] Vitoria Sleep Project No OSA to mod: 0 to 29 Severe: ≥30	NR	25 ischemic strokes: Adjusted HR AHI <30: 1 ref AHI ≥30: 2.52 (1.04 to 6.10), P=0.040	NR	Adjusted only for sex
Saint Martin, 2015[232] Normal or mild: AHI <15 Mod: 15≤AHI≤30 Severe: AHI >30	NR	NR	Attentional Z-Score AHI - t = -3.63, p = 0.0003 Executive Z-Score AHI - t = -0.27, p = 0.45 Memory Z-Score AHI - t = -1.65, p = 0.08 Multiple logistic regression analyses revealed that group 2 (≥ 15 AHI ≤ 30) had no risk for attentional decline (OR, 0.73; 95%	Sex, educational level, baseline age, number of years of follow-up, body mass index, Epworth Sleepiness Scale, hypertension, diabetes, anxiety, and depression

Appendix E Table 33. Results of Prospective Cohort Studies Excluded From KQ 6 Because of Poor Quality That Reported Cardiovascular Events, Cerebrovascular Events, or Cognitive Impairment by AHI

First Author, Year Study Name AHI Cutpoints	Cardiovascular Events, n Events, Adjusted HR/OR (95% CI)	Cerebrovascular Events, n Events, Adjusted HR/OR (95% CI)	Cognitive Impairment, n Events, Adjusted HR/OR (95% CI)	Covariates Included in the Final Adjusted Model (Other Covariates Considered in the Study That Were Not Included in the Final Model)
			confidence interval (CI) = 0.35–1.52, P = 0.40), moderate to severe cases (AHI > 30) were three times more likely to have a greater attentional decline (OR, 2.97; 95% CI, 1.45 to 6.10; P = 0.003).	

Abbreviations: AHI=apnea hypopnea index; BMI=body mass index; CI=confidence interval; HR=hazard ratio; Mod=moderate; NR=not reported; OR=odds ratio; OSA=obstructive sleep apnea; ref=reference; SDB=sleep disordered breathing; WSCS=Wisconsin Sleep Cohort Study.

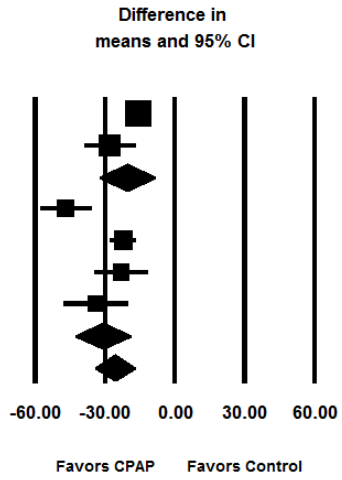
Appendix E Table 34. Results of Randomized, Controlled Trials That Reported Harms (KQ 8) of Mandibular Advancement Devices But Were Excluded Because of Poor Quality

First Author, Year Trial Name	G1 (N) G2 (N)	DC Due to Harms, N (%)	Rash, N (%)	Irritation, N (%)	Need for Addl Sleep Meds, N (%)	Claustro, N (%)	Oral or Nasal Dryness, N (%)	Nosebleed, N (%)	Excess Saliv, N (%)	Pain, N (%)	Dental, N (%)
Blanco, 2005[294]	MAD (12) Sham MAD (12)	3 (25.0) 2 (16.7)	NR	NR	NR	NR	NR	NR	2 (25.0) 0 (0.0)	NR	NR
Mehta, 2001[295]	Total (28) MAD first (NR) Sham MAD first (NR)	2 (7.1) 0 (0.0)	NR	5 (20)	NR	NR	11 (46)	NR	12 (50)	3 (12.5)	3 (12.5)

Abbreviations: addl=additional; claustro=claustrophobia; DC=discontinued: G=group; MAD=mandibular advancement device; N=number; NR=not reported; saliv=salivation.

Appendix F Figure 1. AHI, CPAP vs. Control

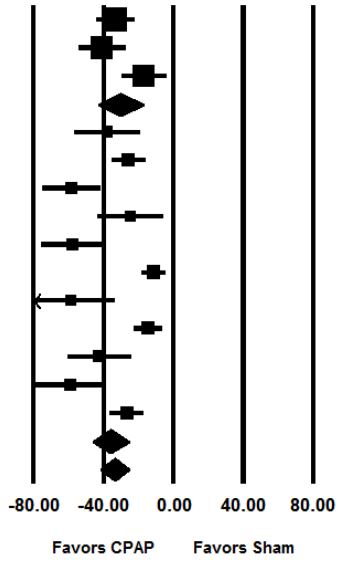
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Control
Crossover	Barnes 2004	12	mil-mod	11	31	21	-15.50	-18.70	-12.30	114	114
Crossover	Toukh, 2012	2	sev only	NR	36	NR	-27.80	-38.53	-17.07	13	13
Crossover							-20.54	-32.40	-8.68		
Parallel	Ip, 2004	4	mod-sev	11	29	47	-46.80	-57.70	-35.90	14	14
Parallel	Lam, 2007	10	mil-sev	12	27	21	-22.20	-27.66	-16.74	34	33
Parallel	Ruttanaumpawan, 2008	4	mod-sev	NR	31	43	-23.00	-34.40	-11.60	19	14
Parallel	Pamidi, 2015	2	mil-sev	11	35	37	-33.90	-47.59	-20.21	26	13
Parallel							-31.02	-42.81	-19.24		
Overall							-25.81	-34.17	-17.45		



Random-effects meta-analyses; overall I-squared=87%

Appendix F Figure 2. AHI, CPAP vs. Sham CPAP

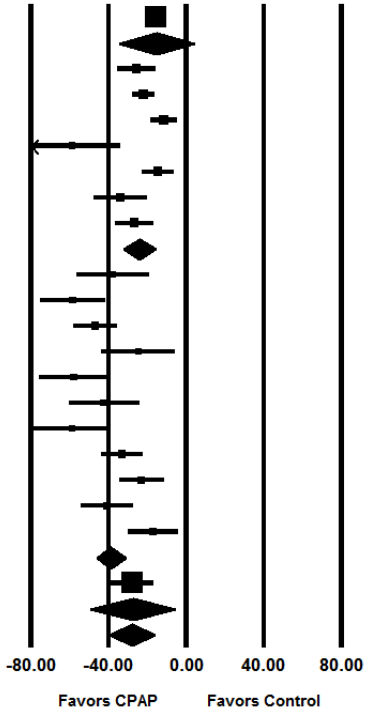
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Sham
Crossover	Phillips, 2011	8	mod-sev	10	32	38	-33.10	-43.77	-22.43	38	38
Crossover	Weinstock, 2012 (P1)	8	mod-sev	NR	39	38	-41.00	-54.31	-27.69	25	25
Crossover	Weinstock, 2012 (P2)	8	mod-sev	NR	39	38	-17.00	-29.57	-4.43	25	25
Crossover							-30.33	-43.49	-17.16		
Parallel	Chasens, 2014	4	mod-sev	11	36	39	-37.85	-56.20	-19.50	12	11
Parallel	Egea, 2008	12	mil-sev	8	32	39	-25.60	-35.20	-16.00	35	38
Parallel	Haensel, 2007	2	mod-sev	NR	33	61	-58.30	-74.88	-41.72	25	25
Parallel	Lam, 2010	1	mod-sev	11	28	40	-24.60	-43.37	-5.83	31	30
Parallel	Loredo, 2006	2	mod-sev	12	32	62	-57.90	-75.70	-40.10	22	19
Parallel	Malow, 2008	<1	mil-sev	NR	34	18	-11.60	-18.18	-5.02	22	15
Parallel	Mills, 2006	2	mil-sev	NR	32	63	-58.50	-83.02	-33.98	17	16
Parallel	Neikrug, 2014	3	mil-sev	NR	28	22	-14.60	-22.59	-6.61	19	19
Parallel	Nguyen, 2010	12	mod-sev	NR	30	36	-42.40	-60.32	-24.48	10	10
Parallel	Norman, 2006	2	mod-sev	12	31	60	-58.90	-78.95	-38.85	18	15
Parallel	Tomfohr, 2011	3	mil-sev	10	30	36	-26.65	-36.19	-17.11	34	37
Parallel							-36.03	-46.51	-25.55		
Overall							-33.82	-42.02	-25.62		



Random-effects meta-analyses; overall I-squared=85%

Appendix F Figure 3. AHI, CPAP vs. Any Inactive, Grouped by OSA Severity

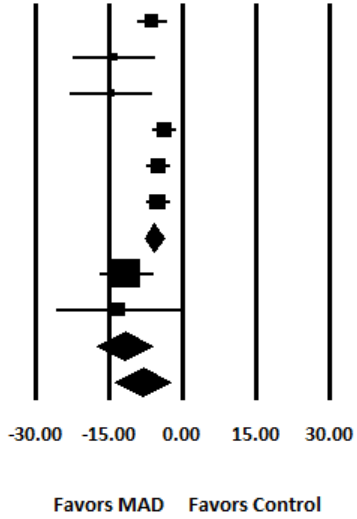
Group by Severity	Study name	Wks	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
mil-mod	Barnes, 2004	12	11	31	21	-15.50	-18.70	-12.30	114	114
mil-mod						-15.50	-34.84	3.84		
mil-sev	Egea, 2008	12	8	32	39	-25.60	-35.20	-16.00	35	38
mil-sev	Lam, 2007	10	12	27	21	-22.20	-27.66	-16.74	34	33
mil-sev	Malow, 2008	<1	NR	34	18	-11.60	-18.18	-5.02	22	15
mil-sev	Mills, 2006	2	NR	32	63	-58.50	-83.02	-33.98	17	16
mil-sev	Neikrug, 2014	3	NR	28	22	-14.60	-22.59	-6.61	19	19
mil-sev	Pamidi, 2015	2	11	35	37	-33.90	-47.59	-20.21	26	13
mil-sev	Tomfohr, 2011	3	10	30	36	-26.65	-36.19	-17.11	34	37
mil-sev						-24.41	-32.70	-16.13		
mod-sev	Chasens, 2014	4	11	36	39	-37.85	-56.20	-19.50	12	11
mod-sev	Haensel, 2007	2	NR	33	61	-58.30	-74.88	-41.72	25	25
mod-sev	Ip, 2004	4	11	29	47	-46.80	-57.70	-35.90	14	14
mod-sev	Lam, 2010	1	11	28	40	-24.60	-43.37	-5.83	31	30
mod-sev	Loredo, 2006	2	12	32	62	-57.90	-75.70	-40.10	22	19
mod-sev	Nguyen, 2010	12	NR	30	36	-42.40	-60.32	-24.48	10	10
mod-sev	Norman, 2006	2	12	31	60	-58.90	-78.95	-38.85	18	15
mod-sev	Phillips, 2011	8	10	32	38	-33.10	-43.77	-22.43	38	38
mod-sev	Ruttanaumpawan, 2008	4	NR	31	43	-23.00	-34.40	-11.60	19	14
mod-sev	Weinstock, 2012 (P1)	8	NR	39	38	-41.00	-54.31	-27.69	25	25
mod-sev	Weinstock, 2012 (P2)	8	NR	39	38	-17.00	-29.57	-4.43	25	25
mod-sev						-39.01	-46.34	-31.67		
sev only	Toukh, 2012	2	NR	36	NR	-27.80	-38.53	-17.07	13	13
sev only						-27.80	-49.68	-5.92		
Overall						-28.10	-39.95	-16.24		



Random-effects meta-analysis; overall I-squared=85%; mil-mod I-squared=0%; mil-sev I-squared=76%; mod-sev I-squared=73%; sev only I-squared=0%

Appendix F Figure 4. AHI, MADs vs. Control

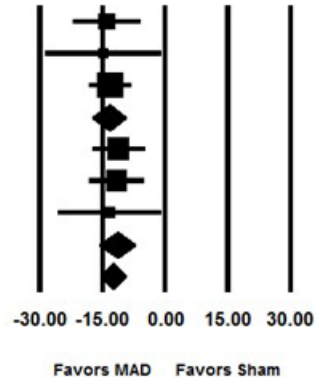
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size		Difference in means and 95% CI
							Difference in means	Lower limit	Upper limit	CPAP	Control	
Crossover	Barnes, 2004	12	mil-mod	11	31	21	-6.30	-9.38	-3.22	114	114	
Crossover	Bloch, 2000a	1	mil-sev	12	27	27	-13.90	-22.32	-5.48	24	24	
Crossover	Bloch, 2000b	1	mil-sev	12	27	27	-14.70	-23.12	-6.28	24	24	
Crossover	Quinnell, 2014a	6	mil-mod	12	31	14	-3.80	-6.36	-1.24	90	90	
Crossover	Quinnell, 2014b	6	mil-mod	12	31	14	-4.90	-7.40	-2.40	90	90	
Crossover	Quinnell, 2014c	6	mil-mod	12	31	14	-5.10	-7.55	-2.65	90	90	
Crossover							-5.85	-7.80	-3.90			
Parallel	Lam, 2007	10	mil-sev	12	27	21	-11.50	-17.02	-5.98	34	33	
Parallel	Petri, 2008	4	mil-sev	11	31	35	-13.10	-25.87	-0.33	33	30	
Parallel							-11.80	-17.52	-6.09			
Overall							-8.20	-13.89	-2.50			



Random-effects meta-analysis; overall I-squared=57%

Appendix F Figure 5. AHI, MADs vs. Sham MAD

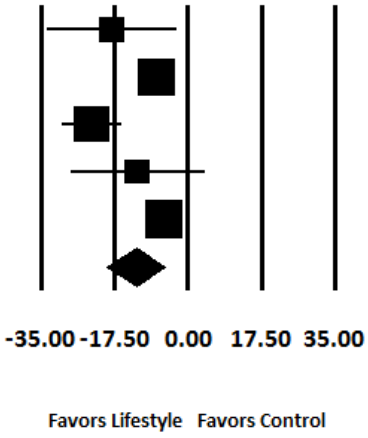
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	MAD	Sham
Crossover	Durán-Cantolla, 2010	12	mil-mod	12	28	15	-14.00	-22.01	-5.99	42	42
Crossover	Johnston, 2002	4 to 6	mil-sev	14	32	32	-14.80	-28.51	-1.09	21	21
Crossover	Naismith, 2005	4	mil-sev	11	29	27	-13.20	-18.13	-8.27	67	67
Crossover							-13.54	-17.55	-9.53		
Parallel	Aarab, 2011	24	mil-mod	11	29	20	-11.10	-17.39	-4.81	21	21
Parallel	Andren, 2013	12	mil-sev	11	31	24	-11.60	-18.22	-4.98	36	36
Parallel	Petri, 2008	4	mil-sev	11	31	35	-13.20	-25.47	-0.93	33	30
Parallel							-11.56	-15.84	-7.29		
Overall							-12.61	-15.54	-9.69		



Random-effects meta-analysis; overall I-squared=0%

Appendix F Figure 6. AHI, Lifestyle Intervention vs. Control

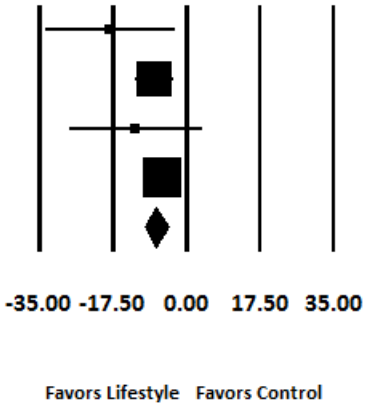
Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Wt loss	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Control
Desplan, 2014	4	mod-sev	11	31	41	BMI -0.8	-18.20	-33.74	-2.66	13	13
Foster, 2009	208	mil-sev	NR	37	23	-5 kg	-7.70	-12.13	-3.27	125	139
Johansson, 2009	9	mod-sev	8	35	37	-20 kg	-23.00	-30.11	-15.89	30	33
Kline, 2012	12	mod-sev	9	35	28	-0.3 kg	-12.10	-27.99	3.79	27	16
Tuomilehto, 2013	260	mild only	10	32	10	-6.1 kg	-5.80	-9.72	-1.88	40	41
							-12.42	-19.38	-5.47		



Random-effects meta-analysis; overall I-squared=79%

Appendix F Figure 7. AHI, Lifestyle Intervention vs. Control, Sensitivity Analysis[a]

Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Wt loss	Statistics for each study			Sample size		Difference in means and 95% CI
							Difference in means	Lower limit	Upper limit	CPAP	Control	
Desplan, 2014	4	mod-sev	11	31	41	BMI -0.8	-18.20	-33.74	-2.66	13	13	
Foster, 2009	208	mil-sev	NR	37	23	-5 kg	-7.70	-12.13	-3.27	125	139	
Kline, 2012	12	mod-sev	9	35	28	-0.3 kg	-12.10	-27.99	3.79	27	16	
Tuomilehto, 2013	260	mild only	10	32	10	-6.1 kg	-5.80	-9.72	-1.88	40	41	
							-7.19	-10.03	-4.36			

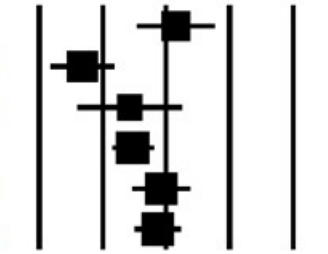


Random-effects meta-analysis; overall I-squared=0%

[*] We found substantial statistical heterogeneity (I^2=79%) in the main analysis, which was no longer present after removing the one study with much larger weight reduction (and with the largest reduction in AHI).

Appendix F Figure 8. AHI, Surgery vs. Control

Study name	Wks	Surgery	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size		Difference in means and 95% CI
							Difference in means	Lower limit	Upper limit	CPAP	Control	
Bäck, 2009	16 to 24	RF surgery	mild only	9	28	12	3.00	-9.01	15.01	17	15	
Browaldh, 2013	28	UPPP	mod-sev	13	28	53	-26.40	-36.19	-16.61	33	34	
Dixon. 2012	104	Bariatric	mod-sev	NR	45	61	-11.50	-27.95	4.95	30	30	
Ferguson, 2003	varied	LAUP	mil-mod	11	32	18	-10.50	-16.88	-4.12	21	25	
Koutsourelakis, 2008	12 to 16	Septoplasty	mil-sev	14	30	32	-1.50	-10.54	7.54	27	22	
Woodson, 2003	8	TCRFTA	mil-mod	13	29	18	-2.70	-9.75	4.35	30	30	



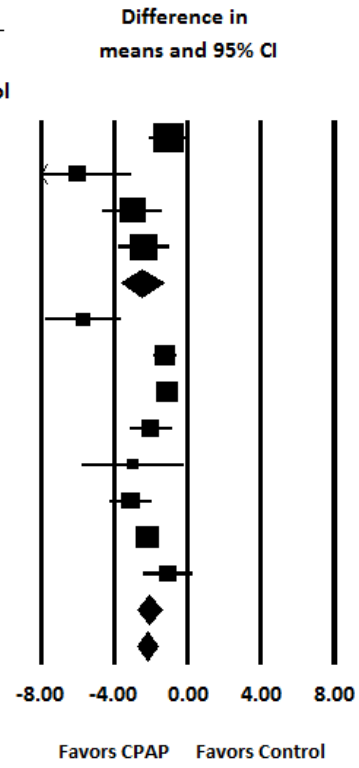
-40.00 -20.00 0.00 20.00 40.00

Favors Surgery Favors Control

Random-effects meta-analysis; overall I-squared=77%; TCRFTA = temperature-controlled radiofrequency tissue ablation

Appendix F Figure 9. ESS, CPAP vs. Control

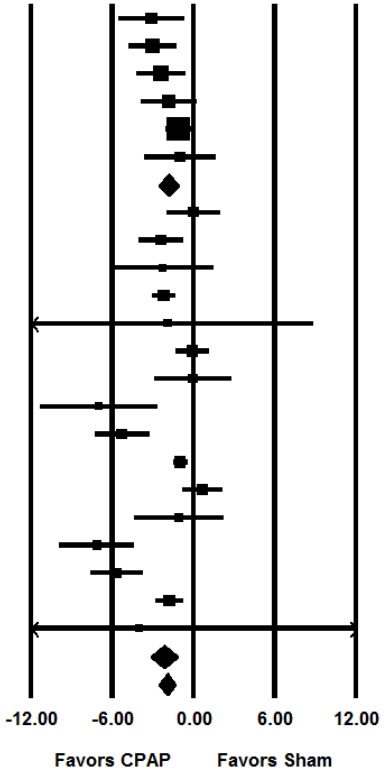
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Control
Cross-over	Barnes, 2004	12	mil-mod	11	31	21	-1.00	-2.09	0.09	114	114
Cross-over	Engleman, 1998	4	mod-sev	12	30	43	-6.00	-8.92	-3.08	23	23
Cross-over	Engleman, 1999	4	mild only	13	30	10	-3.00	-4.64	-1.36	37	37
Cross-over	Faccenda, 2001	4	mod-sev	15	30	35	-2.40	-3.80	-1.00	71	71
Cross-over							-2.47	-3.60	-1.35		
Parallel	Ballester, 1999	12	mod-sev	12	32	56	-5.70	-7.77	-3.63	68	37
Parallel	Barbe, 2010	52	mod-sev	6	33	46	-1.26	-1.91	-0.61	191	183
Parallel	Barbe, 2012	208	mod-sev	7	31	39	-1.10	-1.48	-0.72	357	366
Parallel	Craig, 2012	24	NR	8	33	NR	-2.00	-3.18	-0.82	195	196
Parallel	Lam, 2007	10	mil-sev	12	27	21	-3.00	-5.77	-0.23	34	33
Parallel	Martinez-Garcia, 2013	12	mod-sev	9	34	40	-3.10	-4.27	-1.93	98	96
Parallel	McMillan, 2014	48	mil-sev	12	34	NR	-2.20	-2.28	-2.12	140	138
Parallel	Redline, 1998	8 to 12	mil-mod	11	33	13	-1.09	-2.44	0.26	59	52
Parallel							-2.09	-2.77	-1.41		
Overall							-2.19	-2.78	-1.61		



Random-effects meta-analysis; overall I-squared 84%

Appendix F Figure 10. ESS, CPAP vs. Sham CPAP

Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Sham
Cross-over	Coughlin 2007	6	mod-sev	14	36	40	-3.10	-5.48	-0.72	35	35
Cross-over	Jones, 2013	12	mod-sev	13	30	31	-3.00	-4.74	-1.26	53	53
Cross-over	Marshall 2005	3	mil-mod	13	32	22	-2.40	-4.16	-0.64	31	31
Cross-over	Phillips, 2011	8	mod-sev	10	32	38	-1.80	-3.83	0.23	38	38
Cross-over	Robinson, 2006	4	mil-sev	5	33	NR	-1.10	-2.00	-0.20	35	35
Cross-over	Smith, 2007	6	mod-sev	10	31	36	-1.00	-3.61	1.61	26	26
Cross-over							-1.86	-2.62	-1.10		
Parallel	Barbe, 2001	6	severe only	7	29	56	0.00	-1.93	1.93	29	26
Parallel	Campos-Rodriguez, 2006	4	mil-sev	15	35	59	-2.40	-4.01	-0.79	36	36
Parallel	Chasens, 2014	4	mod-sev	11	36	39	-2.29	-6.02	1.44	12	11
Parallel	Duran-Cantolla, 2010	12	mod-sev	10	32	44	-2.20	-3.00	-1.40	169	171
Parallel	Egea, 2008	12	mil-sev	8	32	39	-1.90	-12.64	8.84	20	25
Parallel	Hoyos, 2012	12	mod-sev	10	32	41	-0.10	-1.29	1.09	34	31
Parallel	Hui, 2006	12	mil-sev	11	27	29	-0.04	-2.88	2.80	28	28
Parallel	Jenkinson, 1999	4	mil-sev	17	35	NR	-7.00	-11.33	-2.67	54	53
Parallel	Kohler, 2008	4	mod-sev	16	35	NR	-5.30	-7.29	-3.31	51	51
Parallel	Kushida, 2012	24	mil-sev	10	32	41	-1.00	-1.50	-0.50	558	547
Parallel	Lam, 2010	1	mod-sev	11	28	40	0.65	-0.76	2.06	31	30
Parallel	Loredo 2006	2	mod-sev	12	32	62	-1.10	-4.34	2.14	22	19
Parallel	Montserrat, 2001	6	mod-sev	17	32	54	-7.15	-9.90	-4.40	24	24
Parallel	Siccoli, 2008	4	mod-sev	16	36	NR	-5.70	-7.62	-3.78	51	51
Parallel	Weaver, 2012	8	mil-mod	15	34	13	-1.78	-2.81	-0.75	121	118
Parallel	West, 2007	12	mil-sev	15	37	NR	-4.00	-23.36	15.36	21	21
Parallel							-2.22	-3.19	-1.25		
Overall							-2.00	-2.59	-1.40		

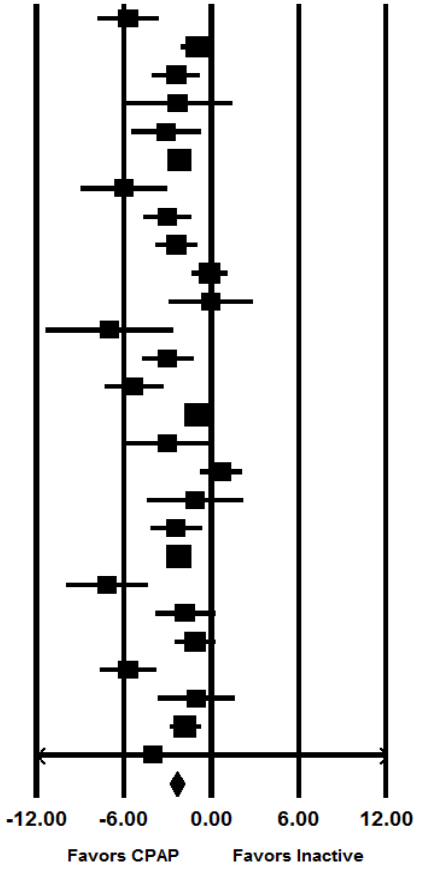


Random-effects meta-analysis; overall I-squared=76%

Appendix F Figure 11. ESS, CPAP vs. Any Inactive, Sensitivity Analysis With Only Studies With Baseline Mean ESS ≥10

Study name	Wks	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
					Difference in means	Lower limit	Upper limit	CPAP	Control
Ballester, 1999	12	12	32	56	-5.70	-7.77	-3.63	68	37
Barnes, 2004	12	11	31	21	-1.00	-2.09	0.09	114	114
Campos-Rodriguez, 2006	4	15	35	59	-2.40	-4.01	-0.79	36	36
Chasens, 2014	4	11	36	39	-2.29	-6.02	1.44	12	11
Coughlin, 2007	6	14	36	40	-3.10	-5.48	-0.72	35	35
Duran-Cantolla, 2010	12	10	32	44	-2.20	-3.00	-1.40	169	171
Engleman, 1998	4	12	30	43	-6.00	-8.92	-3.08	23	23
Engleman, 1999	4	13	30	10	-3.00	-4.64	-1.36	37	37
Faccenda, 2001	4	15	30	35	-2.40	-3.80	-1.00	71	71
Hoyos, 2012	12	10	32	41	-0.10	-1.29	1.09	34	31
Hui, 2006	12	11	27	29	-0.04	-2.88	2.80	28	28
Jenkinson, 1999	4	17	35	NR	-7.00	-11.33	-2.67	54	53
Jones, 2013	12	13	30	31	-3.00	-4.74	-1.26	53	53
Kohler, 2008	4	16	35	NR	-5.30	-7.29	-3.31	51	51
Kushida, 2012	24	10	32	41	-1.00	-1.50	-0.50	558	547
Lam, 2007	10	12	27	21	-3.00	-5.77	-0.23	34	33
Lam, 2010	1	11	28	40	0.65	-0.76	2.06	31	30
Loredo, 2006	2	12	32	62	-1.10	-4.34	2.14	22	19
Marshall, 2005	3	13	32	22	-2.40	-4.16	-0.64	31	31
McMillan, 2014	48	12	34	NR	-2.20	-2.28	-2.12	140	138
Montserrat, 2001	6	17	32	54	-7.15	-9.90	-4.40	24	24
Phillips, 2011	8	10	32	38	-1.80	-3.83	0.23	38	38
Redline, 1998	8 to 12	11	33	13	-1.09	-2.44	0.26	59	52
Siccoli, 2008	4	16	36	NR	-5.70	-7.62	-3.78	51	51
Smith, 2007	6	10	31	36	-1.00	-3.61	1.61	26	26
Weaver, 2012	8	15	34	13	-1.78	-2.81	-0.75	121	118
West, 2007	12	15	37	NR	-4.00	-23.36	15.36	21	21
					-2.37	-2.89	-1.85		

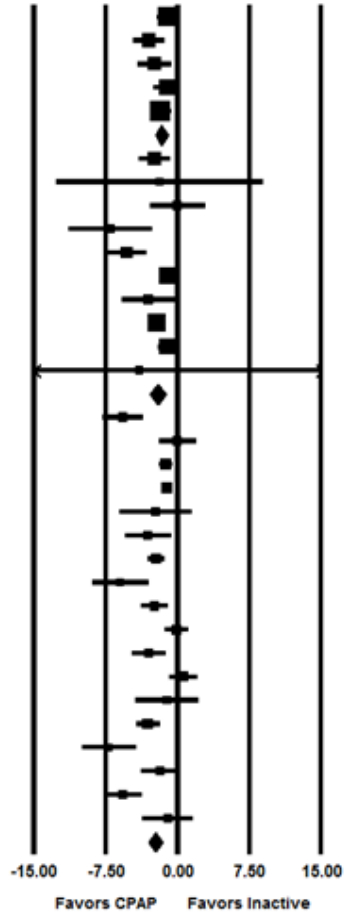
Difference in means and 95% CI



Random-effects meta-analysis; overall I-squared=78%

Appendix F Figure 12. ESS, CPAP vs. Any Inactive, Grouped by OSA Severity

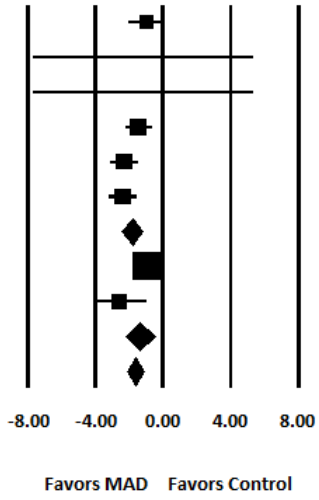
Group by Severity	Study name	Wks	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
mil-mod	Barnes, 2004	12	11	31	21	-1.00	-2.09	0.09	114	114
mil-mod	Engleman, 1999	4	13	30	10	-3.00	-4.64	-1.36	37	37
mil-mod	Marshall, 2005	3	13	32	22	-2.40	-4.16	-0.64	31	31
mil-mod	Redline, 1998	8 to 12	11	33	13	-1.09	-2.44	0.26	59	52
mil-mod	Weaver, 2012	8	15	34	13	-1.78	-2.81	-0.75	121	118
mil-mod						-1.69	-2.38	-1.01		
mil-sev	Campos-Rodriguez, 2006	4	15	35	59	-2.40	-4.01	-0.79	36	36
mil-sev	Egea, 2008	12	8	32	39	-1.90	-12.64	8.84	20	25
mil-sev	Hui, 2006	12	11	27	29	-0.04	-2.88	2.80	28	28
mil-sev	Jenkinson, 1999	4	17	35	NR	-7.00	-11.33	-2.67	54	53
mil-sev	Kohler, 2008	4	16	35	NR	-5.30	-7.29	-3.31	51	51
mil-sev	Kushida, 2012	24	10	32	41	-1.00	-1.50	-0.50	558	547
mil-sev	Lam, 2007	10	12	27	21	-3.00	-5.77	-0.23	34	33
mil-sev	McMillan, 2014	48	12	34	NR	-2.20	-2.28	-2.12	140	138
mil-sev	Robinson, 2006	4	5	33	NR	-1.10	-2.00	-0.20	35	35
mil-sev	West, 2007	12	15	37	NR	-4.00	-23.36	15.36	21	21
mil-sev						-2.14	-2.96	-1.33		
mod-sev	Ballester, 1999	12	12	32	56	-5.70	-7.77	-3.63	68	37
mod-sev	Barbe, 2001	6	7	29	56	0.00	-1.93	1.93	29	26
mod-sev	Barbe, 2010	52	6	33	46	-1.26	-1.91	-0.61	191	183
mod-sev	Barbe, 2012	208	7	31	39	-1.10	-1.48	-0.72	357	366
mod-sev	Chasens, 2014	4	11	36	39	-2.29	-6.02	1.44	12	11
mod-sev	Coughlin, 2007	6	14	36	40	-3.10	-5.48	-0.72	35	35
mod-sev	Duran-Cantolla, 2010	12	10	32	44	-2.20	-3.00	-1.40	169	171
mod-sev	Engleman, 1998	4	12	30	43	-6.00	-8.92	-3.08	23	23
mod-sev	Faccenda, 2001	4	15	30	35	-2.40	-3.80	-1.00	71	71
mod-sev	Hoyos, 2012	12	10	32	41	-0.10	-1.29	1.09	34	31
mod-sev	Jones, 2013	12	13	30	31	-3.00	-4.74	-1.26	53	53
mod-sev	Lam, 2010	1	11	28	40	0.65	-0.76	2.06	31	30
mod-sev	Loredo, 2006	2	12	32	62	-1.10	-4.34	2.14	22	19
mod-sev	Martinez-Garcia, 2013	12	9	34	40	-3.10	-4.27	-1.93	98	96
mod-sev	Montserrat, 2001	6	17	32	54	-7.15	-9.90	-4.40	24	24
mod-sev	Phillips, 2011	8	10	32	38	-1.80	-3.83	0.23	38	38
mod-sev	Siccoli, 2008	4	16	36	NR	-5.70	-7.62	-3.78	51	51
mod-sev	Smith, 2007	6	10	31	36	-1.00	-3.61	1.61	26	26
mod-sev						-2.35	-3.11	-1.60		



Random-effects meta-analysis; overall I-squared=81%; mil-mod I-squared=26%; mil-sev I-squared=79%; mod-sev I-squared=83%

Appendix F Figure 13. ESS, MADs vs. Control

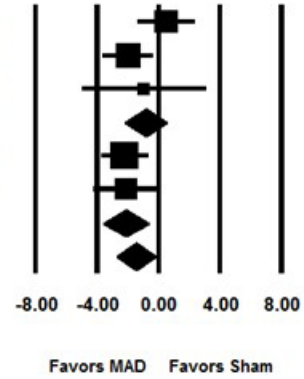
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Crossover	Barnes, 2004	12	mil-mod	11	31	18	-1.00	-2.09	0.09	114	114
Crossover	Bloch, 2000a	1	mil-sev	12	27	27	-1.20	-7.76	5.36	24	24
Crossover	Bloch, 2000b	1	mil-sev	12	27	27	-1.20	-7.76	5.36	24	24
Crossover	Quinnell, 2014a	6	mil-mod	12	31	14	-1.47	-2.27	-0.67	90	90
Crossover	Quinnell, 2014b	6	mil-mod	12	31	14	-2.30	-3.13	-1.47	90	90
Crossover	Quinnell, 2014c	6	mil-mod	12	31	14	-2.41	-3.25	-1.57	90	90
Crossover							-1.83	-2.45	-1.21		
Parallel	Lam, 2007	10	mil-sev	12	27	21	-1.00	-1.49	-0.51	34	33
Parallel	Petri, 2008	4	mil-sev	11	31	35	-2.60	-4.17	-1.03	33	30
Parallel							-1.39	-2.27	-0.50		
Overall							-1.68	-2.19	-1.17		



Random-effects meta-analysis; overall I-squared 52%

Appendix F Figure 14. ESS, MADs vs. Sham MAD

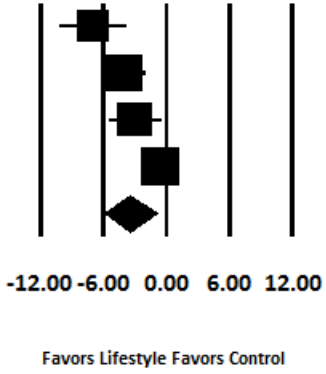
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size		Difference in means and 95% CI
							Difference in means	Lower limit	Upper limit	MAD	Control	
Crossover	Durán-Cantolla, 2010	12	mil-mod	12	28	15	0.50	-1.34	2.34	42	42	
Crossover	Naismith, 2005	4	mil-sev	11	29	27	-2.00	-3.63	-0.37	67	67	
Crossover	Johnston, 2002	4 to 6	mil-sev	14	32	32	-0.95	-4.95	3.05	20	20	
Crossover							-0.86	-2.26	0.53			
Parallel	Andren, 2013	12	mil-sev	11	31	24	-2.20	-3.72	-0.68	36	36	
Parallel	Petri, 2008	4	mil-sev	11	31	35	-2.10	-4.21	0.01	36	30	
Parallel							-2.16	-3.66	-0.66			
Overall							-1.48	-2.75	-0.21			



Random-effects meta-analysis; overall I-squared=34%

Appendix F Figure 15. ESS, Lifestyle Intervention vs. Control

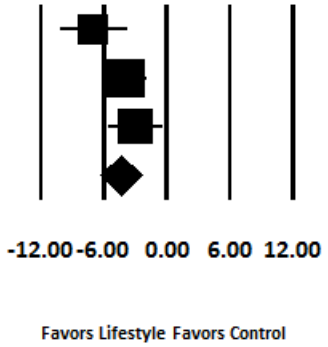
Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Wt loss	Statistics for each study			Sample size		Difference in means and 95% CI
							Difference in means	Lower limit	Upper limit	CPAP	Control	
Desplan, 2014	4	mod-sev	11	31	41	BMI -0.8	-7.00	-10.24	-3.76	13	13	
Johansson, 2009	9	mod-sev	8	35	37	-20 kg	-4.00	-6.01	-1.99	30	33	
Kline, 2012	12	mod-sev	9	35	28	-0.3 kg	-3.00	-5.57	-0.43	27	16	
Tuomilehto, 2013	260	mild only	10	32	10	-6.1 kg	-0.60	-2.35	1.15	40	41	
							-3.43	-5.92	-0.95			



Random effects meta-analysis; overall I-squared 78%

Appendix F Figure 16. ESS, Lifestyle Intervention vs. Control, Sensitivity Analysis[a]

Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Wt loss	Statistics for each study			Sample size		Difference in means and 95% CI
							Difference in means	Lower limit	Upper limit	CPAP	Control	
Desplan, 2014	4	mod-sev	11	31	41	BMI -0.8	-7.00	-10.24	-3.76	13	13	
Johansson, 2009	9	mod-sev	8	35	37	-20 kg	-4.00	-6.01	-1.99	30	33	
Kline, 2012	12	mod-sev	9	35	28	-0.3 kg	-3.00	-5.57	-0.43	27	16	
							-4.42	-6.44	-2.41			

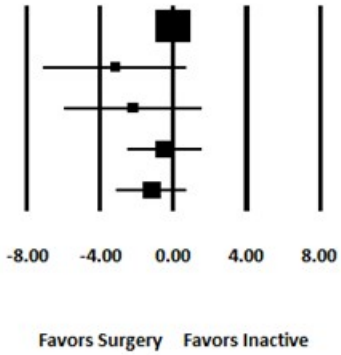


Random effects meta-analysis; overall I-squared 47%

[a] The substantial statistical heterogeneity found in the main analysis was reduced when removing the one trial that enrolled participants with mild OSA.

Appendix F Figure 17. ESS, Surgery vs. Control

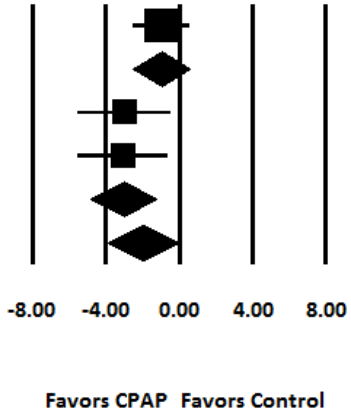
Study name	Wks	Surgery	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Control
Bäck, 2009	16 to 24	RF surgery	mild only	9	28	12	-0.00	-0.00	0.00	17	15
Dixon, 2012	104	Bariatric	mod-sev	NR	45	61	-3.20	-7.12	0.72	30	30
Ferguson, 2003	varied	LAUP	mil-mod	11	32	18	-2.20	-5.96	1.56	21	25
Koutsourelakis	12 to 16	Septoplasty	mil-sev	14	30	32	-0.50	-2.54	1.54	27	22
Woodson, 2003	8	TCRFTA	mil-mod	13	29	18	-1.20	-3.11	0.71	30	30



Random-effects meta-analysis; overall I-squared 52%

Appendix F Figure 18. 24-Hour Mean Arterial Pressure, CPAP vs. Control

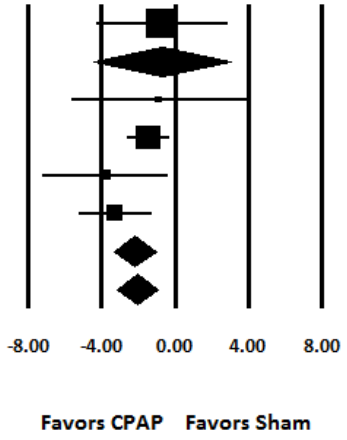
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Control
Crossover	Faccenda, 2001	4	mod-sev	15	30	35	-1.00	-2.59	0.59	71	71
Crossover							-1.00	-2.59	0.59		
Parallel	Gottlieb, 2014	12	mod-sev	9	34	25	-3.00	-5.54	-0.46	106	106
Parallel	Martinez-Garcia, 2013	12	mod-sev	9	34	40	-3.10	-5.58	-0.62	98	96
Parallel							-3.05	-4.83	-1.28		
Overall							-1.99	-3.99	0.02		



Random-effects meta-analysis; overall I-squared 30%

Appendix F Figure 19. 24-Hour Mean Arterial Pressure, CPAP vs. Sham

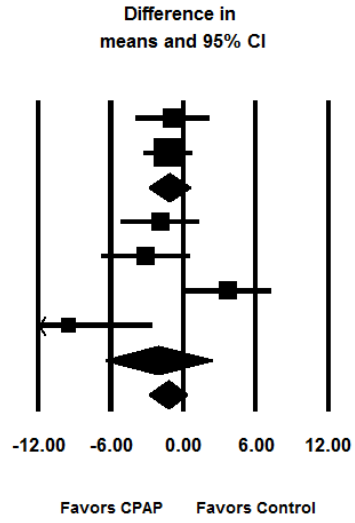
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Control
Cross-over	Robinson, 2006	4	mil-sev	5	33	NR	-0.74	-4.33	2.85	35	35
Cross-over							-0.74	-4.48	3.00		
Parallel	Campos-Rodriguez, 2006	4	mil-sev	15	35	59	-0.90	-5.66	3.86	36	36
Parallel	Duran-Cantolla	12	mod-sev	10	32	44	-1.50	-2.65	-0.35	169	171
Parallel	Hui, 2006	12	mil-sev	11	27	31	-3.80	-7.22	-0.38	28	28
Parallel	Pepperell, 2002	4	mil-sev	16	35	NR	-3.30	-5.28	-1.32	59	59
Parallel							-2.20	-3.37	-1.03		
Overall							-2.07	-3.19	-0.95		



Random-effects meta-analysis; overall I-squared 3%

Appendix F Figure 20. 24-Hour Systolic Blood Pressure, CPAP vs. Control

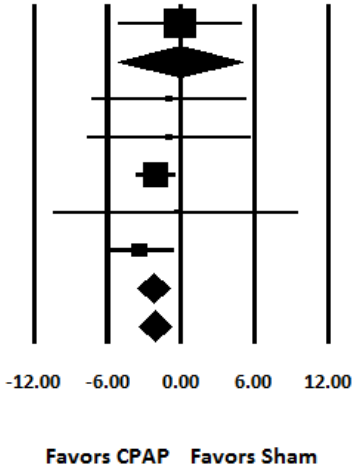
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Control
Cross-over	Barnes, 2004	12	mil-mod	11	31	21	-0.90	-3.93	2.13	114	114
Cross-over	Faccenda, 2001	4	mod-sev	15	30	35	-1.30	-3.28	0.68	71	71
Cross-over							-1.18	-2.84	0.48		
Parallel	Gottlieb, 2014	12	mod-sev	9	34	25	-1.90	-5.13	1.33	106	106
Parallel	Martinez-Garcia, 2013	12	mod-sev	9	34	40	-3.10	-6.73	0.53	98	96
Parallel	McMillan, 2014	48	mil-sev	12	34	NR	3.70	0.19	7.21	140	138
Parallel	Pamidi, 2015	2	mil-sev	11	35	37	-9.50	-16.37	-2.63	26	13
Parallel							-2.08	-6.46	2.29		
Overall							-1.29	-2.85	0.26		



Random-effects meta-analysis; overall I-squared=65%

Appendix F Figure 21. 24-Hour Systolic Blood Pressure, CPAP vs. Sham

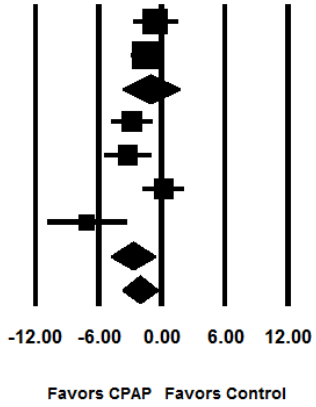
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Control
Cross-over	Robinson, 2006	4	mil-sev	5	33	NR	-0.10	-5.21	5.01	35	35
Cross-over							-0.10	-5.21	5.01		
Parallel	Barbe, 2001	6	sev only	7	29	56	-1.00	-7.35	5.35	29	26
Parallel	Campos-Rodriguez, 2006	4	mil-sev	15	35	59	-1.00	-7.73	5.73	36	36
Parallel	Duran-Cantolla, 2010	12	mod-sev	10	32	44	-2.10	-3.74	-0.46	169	171
Parallel	Hui, 2006	12	mil-sev	11	27	31	-0.40	-10.42	9.62	28	28
Parallel	Pepperell, 2002	4	mil-sev	16	35	NR	-3.40	-6.22	-0.58	59	59
Parallel							-2.27	-3.62	-0.93		
Overall							-2.13	-3.43	-0.83		



Random-effects meta-analysis; overall I-squared 0%

Appendix F Figure 22. 24-Hour Diastolic Blood Pressure, CPAP vs. Control

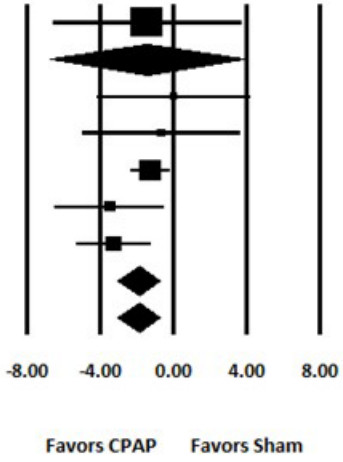
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Cross-over	Barnes, 2004	12	mil-mod	11	31	21	-0.60	-2.72	1.52	114	114
Cross-over	Faccenda, 2001	4	mod-sev	15	30	35	-1.50	-2.94	-0.06	71	71
Cross-over							-1.09	-3.79	1.62		
Parallel	Gottlieb, 2014	12	mod-sev	9	34	25	-2.80	-4.73	-0.87	106	106
Parallel	Martinez-Garcia, 2013	12	mod-sev	9	34	40	-3.20	-5.39	-1.01	98	96
Parallel	McMillan, 2014	48	mil-sev	12	34	NR	0.20	-1.74	2.14	140	138
Parallel	Pamidi, 2015	2	mil-sev	11	35	37	-7.10	-10.82	-3.38	26	13
Parallel							-2.79	-4.86	-0.71		
Overall							-2.16	-3.80	-0.51		



Random-effects meta-analysis; overall I-squared=68%

Appendix F Figure 23. 24-Hour Diastolic Blood Pressure, CPAP vs. Sham

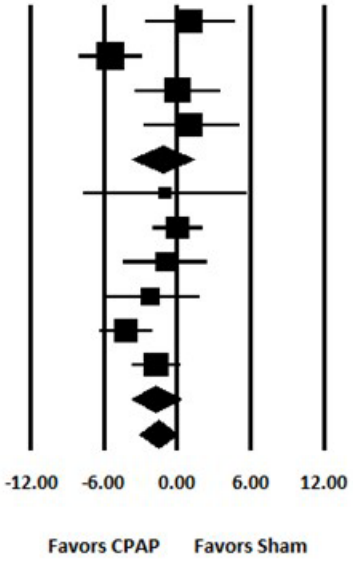
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Cross-over	Robinson, 2006	4	mil-sev	5	33	NR	-1.47	-6.63	3.69	35	35
Cross-over							-1.47	-6.78	3.84		
Parallel	Barbe, 2001	6	sev only	7	29	56	0.00	-4.18	4.18	29	26
Parallel	Campos-Rodriguez, 2006	4	mil-sev	15	35	59	-0.70	-5.02	3.62	36	36
Parallel	Durán-Cantolla, 2010	12	mod-sev	10	32	44	-1.30	-2.39	-0.21	169	171
Parallel	Hui, 2006	12	mil-sev	11	27	31	-3.50	-6.48	-0.52	28	28
Parallel	Pepperell, 2002	4	mil-sev	16	35	NR	-3.30	-5.33	-1.27	59	59
Parallel							-1.93	-3.10	-0.76		
Overall							-1.91	-3.05	-0.77		



Random-effects meta-analysis; overall I-squared 3%

Appendix F Figure 24. Diurnal Mean Arterial Pressure, CPAP vs. Sham

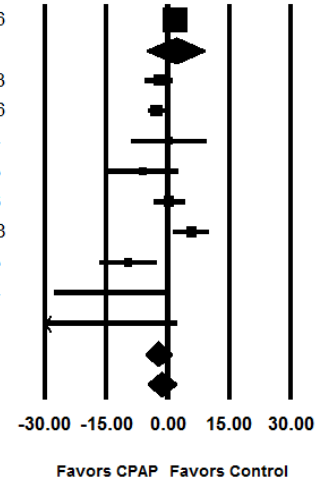
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Crossover	Arias, 2008	12	mil-sev	NR	31	44	1.00	-2.68	4.68	30	30
Crossover	Coughlin, 2007	6	mod-sev	14	36	40	-5.50	-8.15	-2.85	35	35
Crossover	Jones, 2013	12	mod-sev	13	30	31	0.00	-3.56	3.56	53	53
Crossover	Robinson, 2006	4	mil-sev	5	33	NR	1.10	-2.83	5.03	35	35
Crossover							-1.21	-3.74	1.31		
Parallel	Campos-Rodriguez, 2006	4	mil-sev	15	35	15	-1.00	-7.73	5.73	36	36
Parallel	Durán-Cantolla, 2010	12	mod-sev	10	32	44	0.00	-2.03	2.03	169	171
Parallel	Hoyos, 2012	12	mod-sev	10	32	41	-1.01	-4.42	2.40	34	31
Parallel	Hui, 2006	12	mil-sev	11	27	31	-2.20	-6.16	1.76	28	28
Parallel	Pepperell, 2002	4	mil-sev	16	35	NR	-4.20	-6.38	-2.02	59	59
Parallel	Weaver, 2012	8	mil-mod	15	34	13	-1.76	-3.80	0.28	121	118
Parallel							-1.78	-3.76	0.19		
Overall							-1.57	-3.12	-0.01		



Random-effects meta-analysis; overall I-squared 57%

Appendix F Figure 25. Diurnal Systolic Blood Pressure, CPAP vs. Control

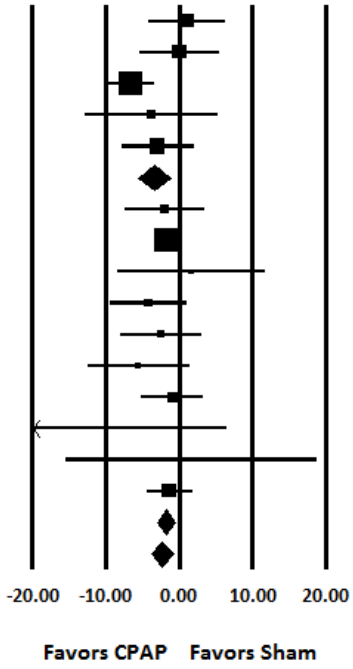
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Cross-over	Craig, 2012	24	NR	8	33	NR	1.80	0.06	3.54	195	196
Cross-over							1.80	-5.34	8.94		
Parallel	Barbe, 2010	52	mod-sev	6	33	46	-2.14	-5.41	1.13	191	183
Parallel	Gottlieb, 2014	12	mod-sev	9	34	25	-2.80	-4.73	-0.87	106	106
Parallel	Ip, 2004	4	mod-sev	11	29	47	0.30	-8.85	9.45	14	14
Parallel	Lam, 2006	10	mil-sev	12	27	21	-6.10	-14.55	2.35	34	33
Parallel	Martinez-Garcia, 2013	12	mod-sev	9	34	40	0.30	-3.43	4.03	98	96
Parallel	McMillan, 2014	48	mil-sev	12	34	NR	5.70	1.46	9.94	140	138
Parallel	Pamidi, 2015	2	mil-sev	11	35	37	-9.70	-16.62	-2.78	26	13
Parallel	Ruttanaumpawan, 2008	4	mod-sev	NR	31	43	-14.00	-27.78	-0.22	19	14
Parallel	Usui, 2005	4	mod-sev	NR	31	33	-19.90	-41.98	2.18	8	9
Parallel							-2.45	-5.61	0.71		
Overall							-1.58	-4.94	1.78		



Random-effects meta-analysis; overall I-squared=75%

Appendix F Figure 26. Diurnal Systolic Blood Pressure, CPAP vs. Sham

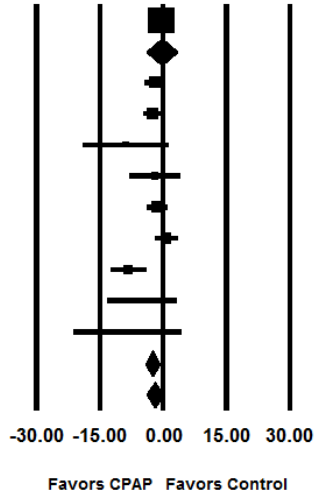
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Cross-over	Arias, 2008	12	mil-sev	NR	31	44	1.00	-4.25	6.25	30	30
Cross-over	Arias, 2005	12	mil-sev	NR	31	44	0.00	-5.44	5.44	27	27
Cross-over	Coughlin, 2007	6	mod-sev	14	36	40	-6.70	-10.04	-3.36	35	35
Cross-over	Cross, 2008	6	mod-sev	NR	37	63	-3.80	-12.80	5.20	29	29
Cross-over	Jones, 2013	12	mod-sev	13	30	31	-3.00	-7.96	1.96	53	53
Cross-over							-3.45	-5.61	-1.28		
Parallel	Barbe, 2001	6	sev only	7	29	56	-2.00	-7.51	3.51	29	26
Parallel	Duran-Cantolla, 2010	12	mod-sev	10	32	44	-1.60	-3.34	0.14	169	171
Parallel	Egea, 2008	12	mil-sev	8	32	39	1.60	-8.44	11.64	20	25
Parallel	Hoyos, 2012	12	mod-sev	10	32	41	-4.25	-9.50	1.00	34	31
Parallel	Hui, 2006	12	mil-sev	11	27	31	-2.50	-8.07	3.07	28	28
Parallel	Kohler, 2008	4	mil-sev	16	35	NR	-5.60	-12.57	1.37	51	51
Parallel	Lam, 2010	1	mod-sev	11	28	40	-0.95	-5.18	3.28	31	30
Parallel	Mills, 2006	2	mil-sev	NR	32	63	-8.00	-22.39	6.39	17	16
Parallel	Nguyen, 2010	12	mod-sev	NR	30	36	1.60	-15.46	18.66	10	10
Parallel	Weaver, 2012	8	mil-mod	15	34	13	-1.32	-4.45	1.81	121	118
Parallel							-1.83	-3.09	-0.57		
Overall							-2.39	-3.89	-0.88		



Random-effects meta-analysis; overall I-squared 0%

Appendix F Figure 27. Diurnal Diastolic Blood Pressure, CPAP vs. Control

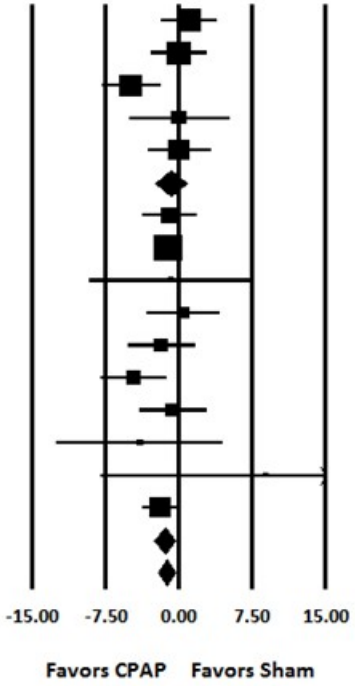
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Cross-over	Craig, 2012	24	NR	8	33	NR	-0.40	-1.50	0.70	195	196
Cross-over							-0.40	-4.01	3.21		
Parallel	Barbe, 2010	52	mod-sev	6	33	46	-1.90	-4.22	0.42	191	183
Parallel	Gottlieb, 2014	12	mod-sev	9	34	25	-2.50	-4.59	-0.41	106	106
Parallel	Ip, 2004	4	mod-sev	11	29	47	-8.90	-18.88	1.08	14	14
Parallel	Lam, 2006	10	mil-sev	12	27	21	-2.00	-7.85	3.85	34	33
Parallel	Martinez-Garcia, 2013	12	mod-sev	9	34	40	-1.50	-3.84	0.84	98	96
Parallel	McMillan, 2014	48	mil-sev	12	34	NR	0.70	-1.98	3.38	140	138
Parallel	Pamidi, 2015	2	mil-sev	11	35	37	-8.20	-12.36	-4.04	26	13
Parallel	Ruttanaumpawan, 2008	4	mod-sev	NR	31	43	-5.00	-13.17	3.17	19	14
Parallel	Usui, 2005	4	mod-sev	NR	31	33	-8.50	-21.13	4.13	8	9
Parallel							-2.65	-4.44	-0.87		
Overall							-2.09	-4.00	-0.19		



Random-effects meta-analysis; overall I-squared=57%

Appendix F Figure 28. Diurnal Diastolic Blood Pressure, CPAP vs. Sham

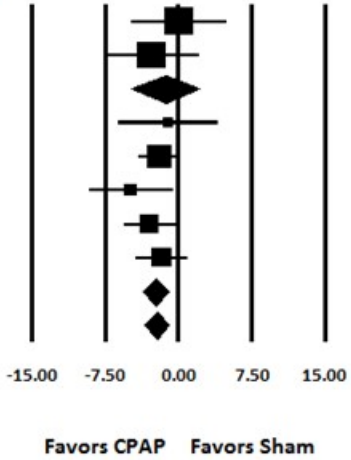
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size		Difference in means and 95% CI
							Difference in means	Lower limit	Upper limit	CPAP	Control	
Cross-over	Arias, 2008	12	mil-sev	NR	31	44	1.00	-1.93	3.93	30	30	
Cross-over	Arias, 2005	12	mil-sev	NR	31	44	0.00	-2.82	2.82	27	27	
Cross-over	Coughlin, 2007	6	mod-sev	14	36	40	-4.90	-7.94	-1.86	35	35	
Cross-over	Cross, 2008	6	mod-sev	NR	37	63	0.00	-5.14	5.14	29	29	
Cross-over	Jones, 2013	12	mod-sev	13	30	31	0.00	-3.25	3.25	53	53	
Cross-over							-0.85	-2.46	0.75			
Parallel	Barbe, 2001	6	sev only	7	29	56	-1.00	-3.76	1.76	29	26	
Parallel	Durán-Cantolla,2010	12	mod-sev	10	32	44	-1.10	-2.30	0.10	169	171	
Parallel	Egea, 2008	12	mil-sev	8	32	39	-0.80	-9.25	7.65	20	25	
Parallel	Hoyos, 2012	12	mod-sev	10	32	41	0.45	-3.31	4.21	34	31	
Parallel	Hui, 2006	12	mil-sev	11	27	31	-1.80	-5.27	1.67	28	28	
Parallel	Kohler, 2008	4	mil-sev	16	35	NR	-4.70	-8.07	-1.33	51	51	
Parallel	Lam, 2010	1	mod-sev	11	28	40	-0.61	-4.08	2.86	31	30	
Parallel	Mills, 2006	2	mil-sev	NR	32	63	-4.00	-12.54	4.54	17	16	
Parallel	Nguyen, 2010	12	mod-sev	NR	30	36	8.90	-8.03	25.83	10	10	
Parallel	Weaver, 2012	8	mil-mod	15	34	13	-1.93	-3.82	-0.04	121	118	
Parallel							-1.47	-2.57	-0.38			
Overall							-1.28	-2.18	-0.37			



Random-effects meta-analysis; overall I-squared 16%

Appendix F Figure 29. Nocturnal Mean Arterial Pressure, CPAP vs. Sham

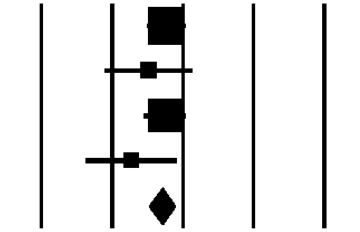
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size		Difference in means and 95% CI
							Difference in means	Lower limit	Upper limit	CPAP	Control	
Crossover	Arias, 2008	12	mil-sev	NR	31	44	0.00	-4.85	4.85	30	30	
Crossover	Robinson, 2006	4	mil-sev	5	33	NR	-2.81	-7.72	2.10	35	35	
Crossover							-1.39	-4.84	2.06			
Parallel	Campos-Rodriguez, 2006	4	mil-sev	15	35	15	-1.10	-6.16	3.96	36	36	
Parallel	Durán-Cantolla, 2010	12	mod-sev	10	32	44	-2.00	-4.18	0.18	169	171	
Parallel	Hui, 2006	12	mil-sev	11	27	31	-4.90	-9.20	-0.60	28	28	
Parallel	Pepperell, 2002	4	mil-sev	16	35	NR	-3.00	-5.67	-0.33	59	59	
Parallel	Weaver, 2012	8	mil-mod	15	34	13	-1.77	-4.41	0.87	121	118	
Parallel							-2.39	-3.69	-1.08			
Overall							-2.26	-3.49	-1.04			

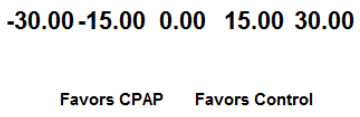


Random-effects meta-analysis; overall I-squared 0%

Appendix F Figure 30. Nocturnal Systolic Blood Pressure, CPAP vs. Control

Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size		Difference in means and 95% CI
						Difference in means	Lower limit	Upper limit	CPAP	Control	
Gottlieb, 2014	12	mod-sev	9	34	25	-3.30	-7.33	0.73	106	106	
Lam, 2007	10	mil-sev	12	27	21	-7.20	-16.40	2.00	34	33	
Martinez-Garcia, 2013	12	mod-sev	9	34	40	-3.70	-8.17	0.77	98	96	
Pamidi, 2015	2	mil-sev	11	35	37	-10.80	-20.42	-1.18	26	13	
						-4.40	-7.13	-1.67			

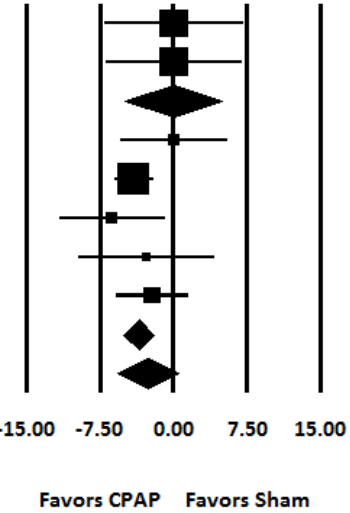




Random-effects meta-analysis; overall I-squared=0%

Appendix F Figure 31. Nocturnal Systolic Blood Pressure, CPAP vs. Sham

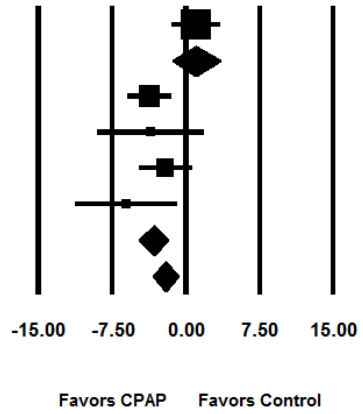
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Cross-over	Arias, 2005	12	mil-sev	NR	31	44	0.00	-7.08	7.08	27	27
Cross-over	Arias, 2008	12	mil-sev	NR	31	44	0.00	-6.91	6.91	30	30
Cross-over							0.00	-4.94	4.94		
Parallel	Barbe, 2001	6	sev only	7	29	56	0.00	-5.51	5.51	29	26
Parallel	Duran-Cantolla, 2010	12	mod-sev	10	32	44	-4.10	-6.09	-2.11	169	171
Parallel	Hui, 2006	12	mil-sev	11	27	31	-6.30	-11.73	-0.87	28	28
Parallel	Kohler, 2008	4	mil-sev	16	35	NR	-2.80	-9.82	4.22	51	51
Parallel	Weaver, 2012	8	mil-mod	15	34	13	-2.21	-5.89	1.47	121	118
Parallel							-3.55	-5.11	-2.00		
Overall							-2.58	-5.68	0.52		



Random-effects meta-analysis; overall I-squared 0%

Appendix F Figure 32. Nocturnal Diastolic Blood Pressure, CPAP vs. Control

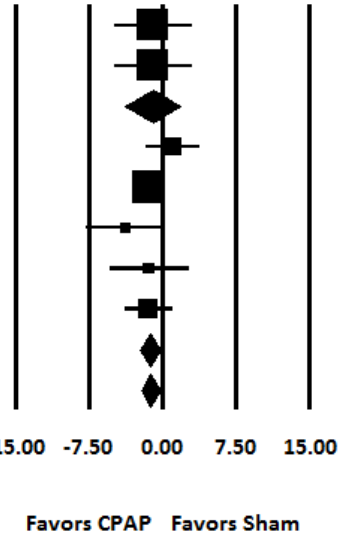
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Control
Cross-over	Barnes, 2004	12	mil-mod	11	31	21	1.00	-1.39	3.39	114	114
Cross-over							1.00	-1.39	3.39		
Parallel	Gottlieb, 2014	12	mod-sev	9	34	25	-3.70	-5.87	-1.53	106	106
Parallel	Lam, 2007	10	mil-sev	12	27	21	-3.60	-8.96	1.76	34	33
Parallel	Martinez-Garcia, 2013	12	mod-sev	9	34	40	-2.10	-4.73	0.53	98	96
Parallel	Pamidi, 2015	2	mil-sev	11	35	37	-6.10	-11.23	-0.97	26	13
Parallel							-3.37	-4.89	-1.84		
Overall							-2.10	-3.39	-0.81		



Random-effects meta-analysis; overall I-squared=64%

Appendix F Figure 33. Nocturnal Diastolic Blood Pressure, CPAP vs. Sham

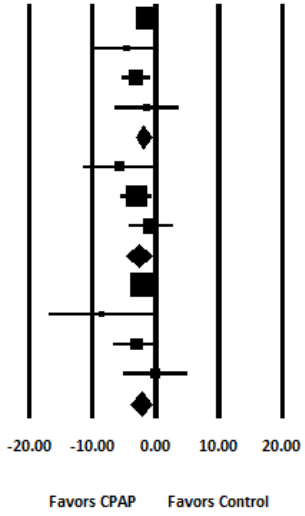
Group by Study Design	Study name	Wks	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size		Difference in means and 95% CI
							Difference in means	Lower limit	Upper limit	CPAP	Control	
Cross-over	Arias, 2005	12	mil-sev	NR	31	44	-1.00	-4.96	2.96	27	27	
Cross-over	Arias, 2008	12	mil-sev	NR	31	44	-1.00	-5.00	3.00	30	30	
Cross-over							-1.00	-3.81	1.81			
Parallel	Barbe, 2001	6	sev only	7	29	56	1.00	-1.76	3.76	29	26	
Parallel	Duran-Cantolla, 2010	12	mod-sev	10	32	44	-1.50	-2.94	-0.06	10	171	
Parallel	Hui, 2006	12	mil-sev	11	27	31	-3.80	-7.91	0.31	28	28	
Parallel	Kohler, 2008	4	mil-sev	16	35	NR	-1.40	-5.44	2.64	51	51	
Parallel	Weaver, 2012	8	mil-mod	15	34	13	-1.51	-3.95	0.93	121	118	
Parallel							-1.28	-2.33	-0.23			
Overall							-1.25	-2.23	-0.26			



Random-effects meta-analysis; overall I-squared 0%

Appendix F Figure 34. 24-Hour Blood Pressure Measures, CPAP vs. Any Inactive in Patients With Hypertension

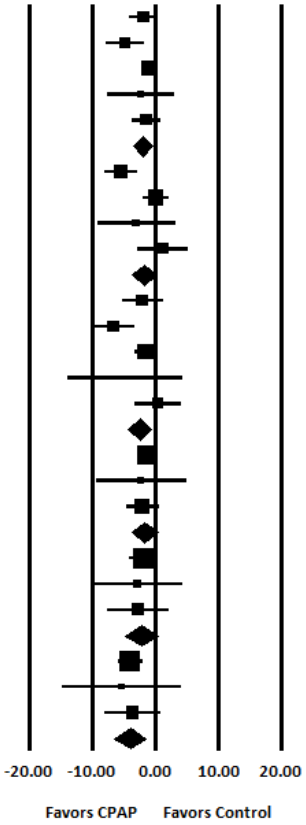
Group by BP outcome	Study name	Control	Wks	Severity	Study Design	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size		Difference in means and 95% CI
									Difference in means	Lower limit	Upper limit	CPAP	Control	
24h DBP	Duran-Cantolla, 2010a	Sham	12	mod-sev	Parallel	10	32	44	-1.30	-2.39	-0.21	169	171	
24h DBP	Hui, 2006a	Sham	12	mil-sev	Parallel	11	27	31	-4.70	-9.75	0.35	17	11	
24h DBP	Martinez-Garcia, 2013a	No tx	12	mod-sev	Parallel	9	34	40	-3.20	-5.39	-1.01	98	96	
24h DBP	Robinson, 2006a	Sham	4	mil-sev	Cross-over	5	33	NR	-1.47	-6.63	3.69	35	35	
24h DBP									-1.99	-3.24	-0.75			
24h MAP	Hui, 2006b	Sham	12	mil-sev	Parallel	11	27	31	-5.70	-11.52	0.12	17	11	
24h MAP	Martinez-Garcia, 2013b	No tx	12	mod-sev	Parallel	9	34	40	-3.10	-5.58	-0.62	98	96	
24h MAP	Robinson, 2006b	Sham	4	mil-sev	Cross-over	5	33	NR	-0.74	-4.33	2.85	35	35	
24h MAP									-2.70	-4.77	-0.63			
24h SBP	Duran-Cantolla, 2010b	Sham	12	mod-sev	Parallel	10	32	44	-2.10	-3.74	-0.46	169	171	
24h SBP	Hui, 2006c	Sham	12	mil-sev	Parallel	11	27	31	-8.60	-17.04	-0.16	17	11	
24h SBP	Martinez-Garcia, 2013c	No tx	12	mod-sev	Parallel	9	34	40	-3.10	-6.73	0.53	98	96	
24h SBP	Robinson, 2006c	Sham	4	mil-sev	Cross-over	5	33	NR	-0.10	-5.21	5.01	35	35	
24h SBP									-2.33	-3.97	-0.69			



Random-effects meta-analysis; I-squared=18% (DBP), 12% (MAP), 3% (SBP)

Appendix F Figure 35. Diurnal and Nocturnal Blood Pressure Measures, CPAP vs. Any Inactive in Patients With Hypertension

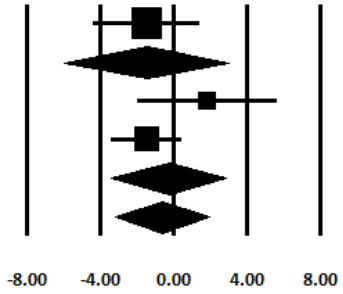
Group by BP outcome	Study name	Control	Wks	Severity	Study Design	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
									Difference in means	Lower limit	Upper limit	CPAP	Control
Day DBP	Barbe, 2010a	Usual care	52	mod-sev	Parallel	6	33	46	-1.90	-4.22	0.42	191	183
Day DBP	Coughlin, 2007a	Sham	6	mod-sev	Cross-over	14	36	40	-4.90	-7.94	-1.86	35	35
Day DBP	Duran-Cantolla, 2010c	Sham	12	mod-sev	Parallel	10	32	44	-1.10	-2.30	0.10	169	171
Day DBP	Hui, 2006d	Sham	12	mil-sev	Parallel	11	27	31	-2.40	-7.74	2.94	17	11
Day DBP	Martinez-Garcia, 2013d	No tx	12	mod-sev	Parallel	9	34	40	-1.50	-3.84	0.84	98	96
Day DBP									-2.06	-3.63	-0.50		
Day MAP	Coughlin, 2007b	Sham	6	mod-sev	Cross-over	14	36	40	-5.50	-8.15	-2.85	35	35
Day MAP	Duran-Cantolla, 2010d	Sham	12	mod-sev	Parallel	10	32	44	0.00	-2.03	2.03	169	171
Day MAP	Hui, 2006e	Sham	12	mil-sev	Parallel	11	27	31	-3.10	-9.25	3.05	17	11
Day MAP	Robinson, 2006d	Sham	4	mil-sev	Cross-over	5	33	NR	1.10	-2.83	5.03	35	35
Day MAP									-1.80	-3.81	0.21		
Day SBP	Barbe, 2010b	Usual care	52	mod-sev	Parallel	6	33	46	-2.14	-5.41	1.13	191	183
Day SBP	Coughlin, 2007c	Sham	6	mod-sev	Cross-over	14	36	40	-6.70	-10.04	-3.36	35	35
Day SBP	Duran-Cantolla, 2010e	Sham	12	mod-sev	Parallel	10	32	44	-1.60	-3.34	0.14	169	171
Day SBP	Hui, 2006f	Sham	12	mil-sev	Parallel	11	27	31	-4.80	-13.95	4.35	17	11
Day SBP	Martinez-Garcia, 2013e	No tx	12	mod-sev	Parallel	9	34	40	0.30	-3.43	4.03	98	96
Day SBP									-2.53	-4.37	-0.68		
Noct DBP	Duran-Cantolla, 2010f	Sham	12	mod-sev	Parallel	10	32	44	-1.50	-2.94	-0.06	10	171
Noct DBP	Hui, 2006g	Sham	12	mil-sev	Parallel	11	27	31	-2.30	-9.45	4.85	17	11
Noct DBP	Martinez-Garcia, 2013f	No tx	12	mod-sev	Parallel	9	34	40	-2.10	-4.73	0.53	98	96
Noct DBP									-1.77	-3.90	0.35		
Noct MAP	Duran-Cantolla, 2010g	Sham	12	mod-sev	Parallel	10	32	44	-2.00	-4.18	0.18	169	171
Noct MAP	Hui, 2006h	Sham	12	mil-sev	Parallel	11	27	31	-2.90	-10.10	4.30	17	11
Noct MAP	Robinson, 2006e	Sham	4	mil-sev	Cross-over	5	33	NR	-2.81	-7.72	2.10	35	35
Noct MAP									-2.29	-4.92	0.33		
Noct SBP	Duran-Cantolla, 2010h	Sham	12	mod-sev	Parallel	10	32	44	-4.10	-6.09	-2.11	169	171
Noct SBP	Hui, 2006i	Sham	12	mil-sev	Parallel	11	27	31	-5.40	-14.94	4.14	17	11
Noct SBP	Martinez-Garcia, 2013h	No tx	12	mod-sev	Parallel	9	34	40	-3.70	-8.17	0.77	98	96
Noct SBP									-4.09	-6.66	-1.51		



Random-effects meta-analysis; I-squared=25% (Day DBP), 76% (Day MAP), 58% (Day SBP), 0% (Noct DBP, MAP, SBP)

Appendix F Figure 36. 24-Hour Systolic Blood Pressure, MADs vs. Any Inactive

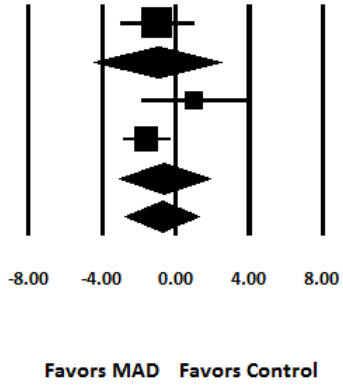
Group by Comparator	Study name	Wks	Study Design	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Control	Barnes, 2004	12	Crossover	mil-mod	11	31	18	-1.50	-4.38	1.38	114	114
Control								-1.50	-5.97	2.97		
Sham	Andren, 2013	12	Parallel	mil-sev	11	30	24	1.80	-2.03	5.63	36	36
Sham	Gotsopoulos, 2004	4	Crossover	mil-sev	11	29	27	-1.50	-3.43	0.43	67	67
Sham								-0.28	-3.40	2.84		
Overall								-0.68	-3.24	1.88		



Random-effects meta-analysis; overall I-squared=17%

Appendix F Figure 37. 24-Hour Diastolic Blood Pressure, MADs vs. Any Inactive

Group by Comparator	Study name	Wks	Study Design	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Control	Barnes, 2004	12	Crossover	mil-mod	11	31	18	-1.00	-3.06	1.06	114	114
Control								-1.00	-4.51	2.51		
Sham	Andren, 2013	12	Parallel	mil-sev	11	30	24	1.00	-1.85	3.85	36	36
Sham	Gotsopoulos, 2004	4	Crossover	mil-sev	11	29	27	-1.60	-2.89	-0.31	67	67
Sham								-0.62	-3.09	1.84		
Overall								-0.75	-2.77	1.27		



Random-effects meta-analysis; overall I-squared=25%

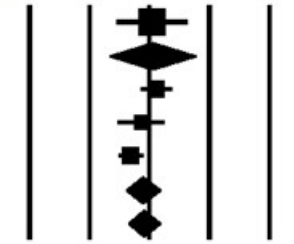
Appendix F Figure 38. Diurnal Systolic Blood Pressure, MADs vs. Any Inactive

Group by Comparator	Study name	Wks	Study Design	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size		Difference in means and 95% CI
								Difference in means	Lower limit	Upper limit	MAD	Control	
Control	Lam, 2007	10	Parallel	mil-sev	12	27	21	-2.40	-11.58	6.78	34	33	
Control								-2.40	-12.45	7.65			
Sham	Andren, 2013	12	Parallel	mil-sev	11	30	24	1.80	-2.08	5.68	36	36	
Sham	Durán-Cantolla, 2010	12	Crossover	mil-mod	12	28	15	-2.30	-8.67	4.07	42	42	
Sham	Gotsopoulos, 2004	4	Crossover	mil-sev	11	29	27	-3.00	-5.63	-0.37	67	67	
Sham								-1.21	-4.52	2.09			
Overall								-1.33	-4.47	1.81			

Random-effects meta-analysis; overall I-squared=27%

Appendix F Figure 39. Diurnal Diastolic Blood Pressure, MADs vs. Any Inactive

Group by Comparator	Study name	Wks	Study Design	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size		Difference in means and 95% CI
								Difference in means	Lower limit	Upper limit	CPAP	Control	
Control	Lam, 2007	10	Parallel	mil-sev	12	27	21	0.40	-5.48	6.28	34	33	
Control								0.40	-6.76	7.56			
Sham	Andren, 2013	12	Parallel	mil-sev	11	30	24	1.20	-1.40	3.80	36	36	
Sham	Durán-Cantolla, 2010	12	Crossover	mil-mod	12	28	15	-1.40	-5.26	2.46	42	42	
Sham	Gotsopoulos, 2004	4	Crossover	mil-sev	11	29	27	-3.10	-5.13	-1.07	67	67	
Sham								-1.16	-4.02	1.70			
Overall								-0.95	-3.60	1.71			



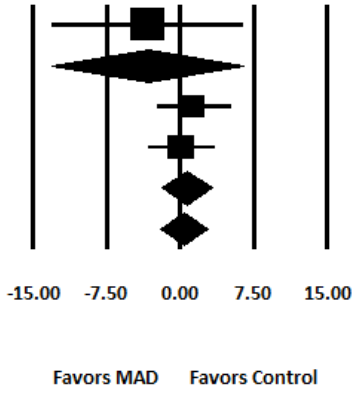
-20.00 -10.00 0.00 10.00 20.00

Favors MAD Favors Control

Random-effects meta-analysis; overall I-squared=56%

Appendix F Figure 40. Nocturnal Systolic Blood Pressure, MADs vs. Any Inactive

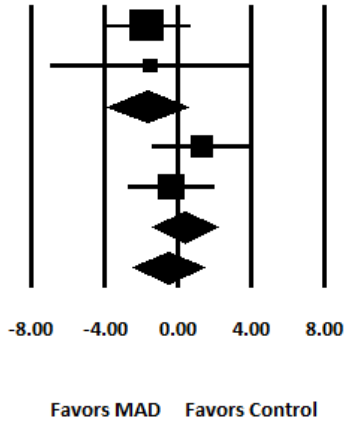
Group by Comparator	Study name	Wks	Study Design	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study			Sample size	
								Difference in means	Lower limit	Upper limit	CPAP	Control
Control	Lam, 2007	10	Parallel	mil-sev	12	27	21	-3.30	-13.06	6.46	34	33
Control								-3.30	-13.06	6.46		
Sham	Andren, 2013	12	Parallel	mil-sev	11	30	24	1.40	-2.43	5.23	36	36
Sham	Gotsopoulos, 2004	4	Crossover	mil-sev	11	29	27	0.10	-3.27	3.47	67	67
Sham								0.67	-1.86	3.20		
Overall								0.42	-2.03	2.87		



Random-effects meta-analysis; overall I-squared=0%

Appendix F Figure 41. Nocturnal Diastolic Blood Pressure, MADs vs. Any Inactive

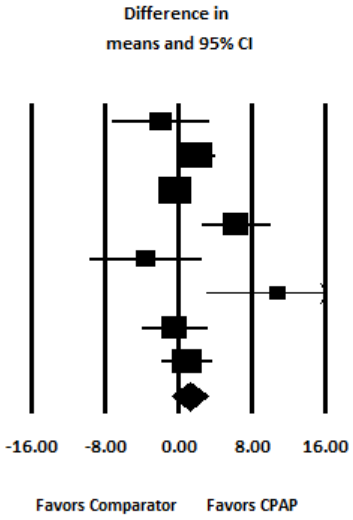
Group by Comparator	Study name	Wks	Study Design	Severity	BL ESS	BL BMI	BL AHI	Statistics for each study: Difference in means	Lower limit	Upper limit	Sample size: CPAP	Control
Control	Barnes, 2004	12	Crossover	mil-mod	11	31	18	-1.70	-4.07	0.67	114	114
Control	Lam, 2007	10	Parallel	mil-sev	12	27	21	-1.50	-7.01	4.01	34	33
Control								-1.67	-3.84	0.51		
Sham	Andren, 2013	12	Parallel	mil-sev	11	30	24	1.30	-1.45	4.05	36	36
Sham	Gotsopoulos, 2004	4	Crossover	mil-sev	11	29	27	-0.40	-2.78	1.98	67	67
Sham								0.33	-1.47	2.13		
Overall								-0.57	-2.52	1.37		



Random-effects meta-analysis; overall I-squared=0%

Appendix F Figure 42. Short-Form (36-Item) Health Survey Mental Component Summary, CPAP vs. Inactive Control

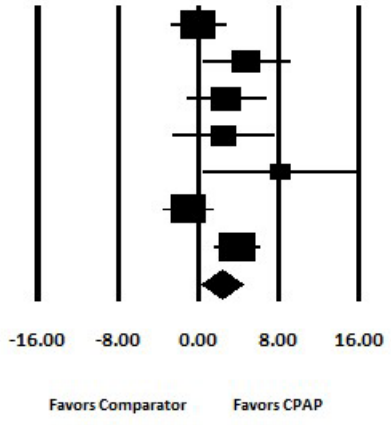
Study name	Wks	Severity	BL ESS	BL AHI	Study Design	Comparator	Statistics for each study			Sample size	
							Difference in means	Lower limit	Upper limit	CPAP	Control
Barbe, 2001	6	sev only	7	56	Parallel	Sham	-2.00	-7.29	3.29	29	26
Craig, 2012	24	NR	8	NR	Parallel	Control	1.90	-0.21	4.01	195	196
Egea, 2008	12	mil-sev	8	39	Parallel	Sham	-0.50	-1.69	0.69	35	38
Jenkinson, 1999	4	mil-mod	17	NR	Parallel	Sham	6.20	2.48	9.92	54	53
Montserrat, 2001	6	mod-sev	17	54	Parallel	Sham	-3.60	-9.71	2.51	24	24
Siccoli, 2008	4	mod-sev	16	NR	Parallel	Sham	10.80	2.91	18.69	51	51
Smith, 2007	6	mod-sev	10	36	Crossover	Sham	-0.50	-4.10	3.10	24	24
Weaver, 2012	8	mil-mod	15	13	Parallel	Sham	0.86	-1.94	3.66	121	118
							1.19	-0.84	3.23		



Random-effects meta-analysis; overall I-squared 69%

Appendix F Figure 43. Short-Form (36-Item) Health Survey Physical Component Summary, CPAP vs. Inactive Control

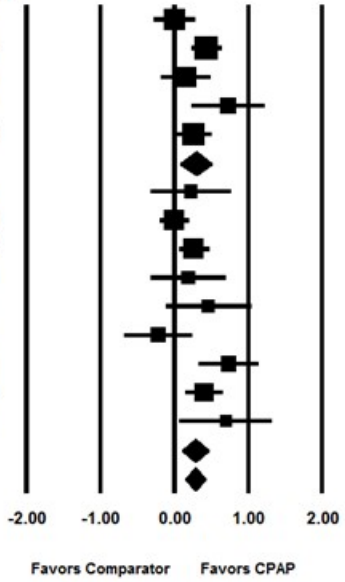
Study name	Wks	Severity	BL ESS	BL AHI	Study Design	Comparator	Statistics for each study			Sample size		Difference in means and 95% CI
							Difference in means	Lower limit	Upper limit	CPAP	Control	
Barbe, 2001	6	sev only	7	56	Parallel	Sham	0.00	-2.76	2.76	29	26	
Egea, 2008	12	mil-sev	8	39	Parallel	Sham	4.80	0.39	9.21	35	38	
Jenkinson, 1999	4	mil-mod	12	NR	Parallel	Sham	2.80	-1.22	6.82	54	53	
Montserrat, 2001	6	mod-sev	17	54	Parallel	Sham	2.56	-2.56	7.68	24	24	
Siccoli, 2008	4	mod-sev	16	NR	Parallel	Sham	8.20	0.52	15.88	51	51	
Smith, 2007	6	mod-sev	10	36	Crossover	Sham	-1.00	-3.53	1.53	24	24	
Weaver, 2012	8	mil-mod	15	13	Parallel	Sham	3.85	1.54	6.16	121	118	
							2.29	0.21	4.37			



Random-effects meta-analysis; overall I-squared 57%

Appendix F Figure 44. Sleep-Related Quality of Life, CPAP vs. Inactive Control[a]

Group by Comparator	Study name	Wks	Severity	BL ESS	BL AHI	Study Design	Statistics for each study: Std diff in means	Lower limit	Upper limit	Sample size: CPAP	Control
Control	Barnes, 2004	12	mil-mod	8	21	Crossover	0.00	-0.28	0.28	97	97
Control	Craig, 2012	24	NR	8	NR	Parallel	0.43	0.23	0.63	195	196
Control	Facenda, 2001	4	mod-sev	15	35	Crossover	0.16	-0.17	0.49	71	71
Control	Lam, 2007	10	mil-sev	12	21	Crossover	0.73	0.24	1.22	34	34
Control	McMillian, 2014	52	mil-sev	12	NR	Parallel	0.26	0.02	0.50	140	138
Control							0.29	0.07	0.50		
Sham	Barbe, 2001	6	sev only	7	56	Parallel	0.22	-0.31	0.75	29	26
Sham	Batool-Anwar, 2016a	24	mil-sev	10	40	Parallel	0.00	-0.19	0.19	193	242
Sham	Batool-Anwar, 2016b	24	mil-sev	10	40	Parallel	0.26	0.07	0.46	249	160
Sham	Marshall, 2005	3	mil-mod	13	22	Crossover	0.19	-0.31	0.69	31	31
Sham	Montserrat, 2001	6	mod-sev	17	54	Parallel	0.46	-0.11	1.03	24	24
Sham	Phillips, 2011	8	mod-sev	8	38	Crossover	-0.22	-0.67	0.23	38	38
Sham	Siccoli, 2008	4	mod-sev	16	NR	Parallel	0.73	0.33	1.13	51	51
Sham	Weaver, 2012	8	mil-mod	15	13	Parallel	0.40	0.16	0.65	141	118
Sham	West, 2007	12	mil-sev	15	NR	Parallel	0.70	0.07	1.32	21	21
Sham							0.27	0.09	0.45		
Overall							0.28	0.14	0.42		

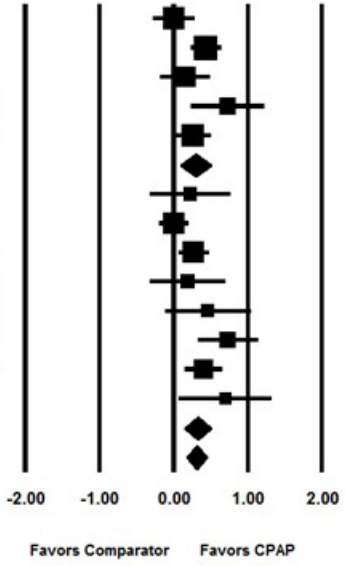


Random-effects meta-analysis; overall I-squared=58%

[*] Batool-Anwar, 2016a data are from participants with CPAP (or sham) compliance < 4 hours; Batool-Anwar, 2016b data are from participants with compliance >4 hours.

Appendix F Figure F45. Sleep-Related Quality of Life, CPAP vs. Inactive Control; Sensitivity Analysis Without Phillips[a]

Group by Comparator	Study name	Wks	Severity	BL ESS	BL AHI	Study Design	Statistics for each study			Sample size	
							Std diff in means	Lower limit	Upper limit	CPAP	Control
Control	Barnes, 2004	12	mil-mod	8	21	Crossover	0.00	-0.28	0.28	97	97
Control	Craig, 2012	24	NR	8	NR	Parallel	0.43	0.23	0.63	195	196
Control	Facenda, 2001	4	mod-sev	15	35	Crossover	0.16	-0.17	0.49	71	71
Control	Lam, 2007	10	mil-sev	12	21	Crossover	0.73	0.24	1.22	34	34
Control	McMillian, 2014	52	mil-sev	12	NR	Parallel	0.26	0.02	0.50	140	138
Control							0.29	0.08	0.49		
Sham	Barbe, 2001	6	sev only	7	56	Parallel	0.22	-0.31	0.75	29	26
Sham	Batool-Anwar, 2016a	24	mil-sev	10	40	Parallel	0.00	-0.19	0.19	193	242
Sham	Batool-Anwar, 2016b	24	mil-sev	10	40	Parallel	0.26	0.07	0.46	249	160
Sham	Marshall, 2005	3	mil-mod	13	22	Crossover	0.19	-0.31	0.69	31	31
Sham	Montserrat, 2001	6	mod-sev	17	54	Parallel	0.46	-0.11	1.03	24	24
Sham	Siccoli, 2008	4	mod-sev	16	NR	Parallel	0.73	0.33	1.13	51	51
Sham	Weaver, 2012	8	mil-mod	15	13	Parallel	0.40	0.16	0.65	141	118
Sham	West, 2007	12	mil-sev	15	NR	Parallel	0.70	0.07	1.32	21	21
Sham							0.32	0.14	0.50		
Overall							0.31	0.17	0.44		

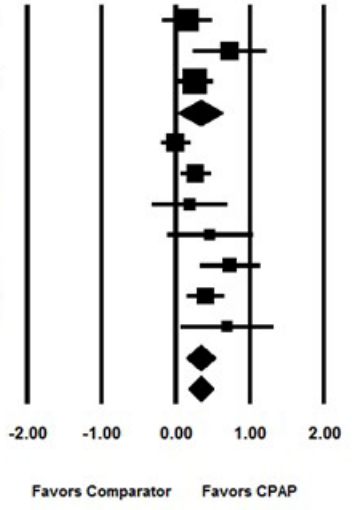


Random-effects meta-analysis; overall I-squared=54%

[*] Batool-Anwar, 2016a data are from participants with CPAP (or sham) compliance < 4 hours; Batool-Anwar, 2016b data are from participants with compliance >4 hours.

Appendix F Figure 46. Sleep-Related Quality of Life, CPAP vs. Inactive Control; Sensitivity Analysis Including Only Studies With Mean Baseline ESS ≥10

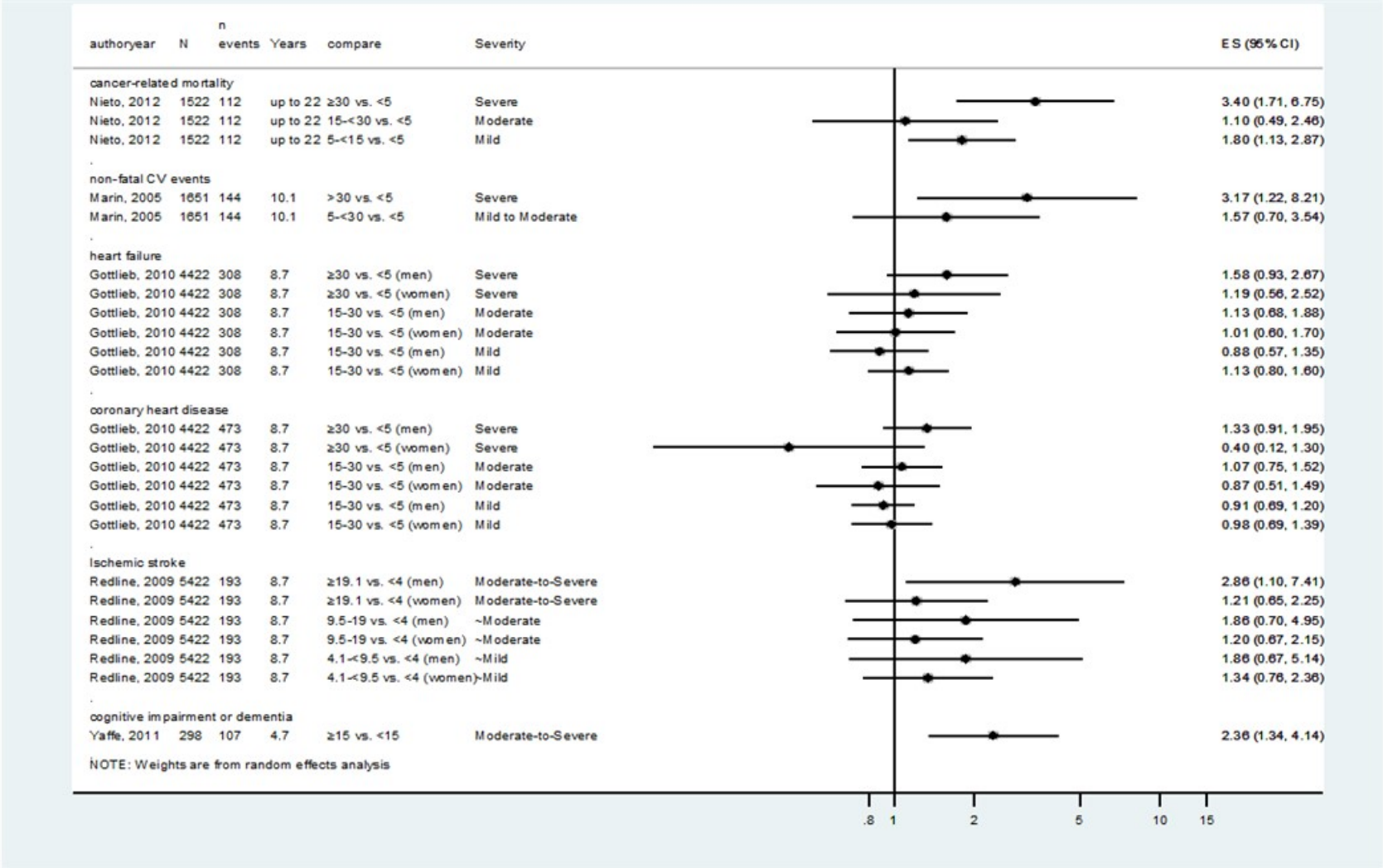
Group by Comparator	Study name	Wks	Severity	BL ESS	BL AHI	Study Design	Statistics for each study			Sample size		Std diff in means and 95% CI
							Std diff in means	Lower limit	Upper limit	CPAP	Control	
Control	Facenda, 2001	4	mod-sev	15	35	Crossover	0.16	-0.17	0.49	71	71	
Control	Lam, 2007	10	mil-sev	12	21	Crossover	0.73	0.24	1.22	34	34	
Control	McMillian, 2014	52	mil-sev	12	NR	Parallel	0.26	0.02	0.50	140	138	
Control							0.33	0.04	0.63			
Sham	Batool-Anwar, 2016a	24	mil-sev	10	40	Parallel	0.00	-0.19	0.19	193	242	
Sham	Batool-Anwar, 2016b	24	mil-sev	10	40	Parallel	0.26	0.07	0.46	249	160	
Sham	Marshall, 2005	3	mil-mod	13	22	Crossover	0.19	-0.31	0.69	31	31	
Sham	Montserrat, 2001	6	mod-sev	17	54	Parallel	0.46	-0.11	1.03	24	24	
Sham	Siccoli, 2008	4	mod-sev	16	NR	Parallel	0.73	0.33	1.13	51	51	
Sham	Weaver, 2012	8	mil-mod	15	13	Parallel	0.40	0.16	0.65	141	118	
Sham	West, 2007	12	mil-sev	15	NR	Parallel	0.70	0.07	1.32	21	21	
Sham							0.34	0.14	0.53			
Overall							0.33	0.17	0.50			



Random-effects meta-analysis; overall I-squared=56%

* Batool-Anwar, 2016a data are from participants with CPAP (or sham) compliance < 4 hours; Batool-Anwar, 2016b data are from participants with compliance >4 hours.

Appendix F Figure 47. Association Between AHI and Cancer-Related Mortality, Cardiovascular Events, Stroke, and Cognitive Impairment or Dementia



1a. What is the rate of adherence to CPAP, mandibular advancement devices, and weight loss interventions among persons with OSA?
1b. How effective are interventions designed to enhance adherence to CPAP?

CQ1 is addressed in the Discussion, last paragraph under "Benefits and Harms of Treatment for OSA" (pg 37). That entire paragraph is related to CQ 1a and 1b. Briefly, a wide range of adherence to CPAP usage recommendations has been reported, ranging from about 30 to 85 percent. A systematic review reported that 14 to 32 percent of patients discontinue CPAP over 4 years and patients use CPAP for an average of 5 hours per night; data were too limited to provide adherence rates for MADs. A recent Cochrane systematic review of 33 studies (2,047 participants) found low- to moderate-quality evidence that three types of interventions can increase CPAP machine usage in CPAP-naive participants with moderate to severe OSA syndrome. However, they noted that trials did not assess people who have struggled to adhere to treatment and the impact of improved CPAP usage on daytime sleepiness, quality of life, and long-term cardiovascular risks remains unclear.

For weight loss interventions, a wide range of adherence has been reported. A systematic review of interventions for improving nutrition and physical activity behaviors reported that adherence to attending intervention programs ranged from 33.0 percent to 95.0 percent and that retention rates ranged from 43 percent to 96 percent (mean 80%).[296] The review for the USPSTF on behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults noted that most trials did not report adherence to interventions.[297] The review for the USPSTF on counseling to promote a healthy lifestyle in persons with cardiovascular risk factors[298] noted that many intensive combined lifestyle and diet-only interventions would require resources that are not currently available or paid for and that "…fidelity of and adherence to counseling interventions should be routinely reported to better understand the applicability of behavioral counseling trial findings". A systematic review that reported adherence to self-monitoring activities in weight loss interventions[299] noted that "detailed measurement of adherence to self-monitoring has been reported infrequently; thus, little is known about the extent to which people adhere over time." It concluded that the variability in measurement methods (for adherence) made it impossible to compare adherence across studies. Data from years 1 and 5 of the Women's Health Initiative Dietary Modification Trial (N~50,000), in which participants were randomly assigned to a low-fat dietary intervention arm or usual diet control arm, suggest that long-term dietary change can be achieved (although it was in a clinical trial setting). The authors reported adherence to a low-fat dietary pattern (less than 20% energy from fat, five or more fruit/vegetable and six or more grain servings daily) assessed as the difference between groups in percent total energy from fat. The difference was 10.9 percentage points of energy from fat at Year 1 and 9.0 at Year 5.

2. What are the barriers to undergoing diagnostic testing for OSA (e.g., availability of polysomnography, ability to tolerate testing)? How often do those barriers prevent completion of testing?

CQ2 is addressed in the Discussion, second paragraph under "Accuracy and Reliability of Diagnostic Tests" (pg 35). That entire paragraph is related to CQ 2. Briefly, barriers

include limited availability of PSG, ability to tolerate testing, inconvenience, and costs. It is unclear how often those barriers prevent completion of testing. Mean time from referral to sleep clinic evaluation ranges from a few weeks to more than a year, with longer wait times for university, state, and federal government sleep lab facilities.

3. Is there an association between reduction in sleepiness and quality of life, work productivity, motor vehicle crashes, or other health outcomes?

   Some information related to this CQ was within 1 study in the results for KQ 6 (because one study assessing the relationship between AHI and all-cause mortality evaluated subgroups based on sleepiness). That study (last paragraph under the All-cause Mortality header in KQ 6, pg 28) found that the association between AHI ≥20 and death was limited to those with excessive daytime sleepiness (determined by self-report of having a problem with feeling sleepy or struggling to stay awake during the daytime ≥3 or 4 times a week) but was not significant for those without excessive daytime sleepiness (HR, 2.28; 95% CI, 1.46 to 3.57 vs. HR, 0.74; 95% CI, 0.39 to 1.38) compared with a reference group with AHI <20 and no excessive daytime sleepiness.

   CQ 3 is addressed also in the Discussion in under "Benefits and Harms of Treatment for OSA" (pg 35-36). One publication that used the nation-wide population-based Sleep Heart Health Study (SHHS) (n=5,816; mean age=63 years; 52.5% women) reported that EDS was strongly associated with reduced QoL even after adjusting for confounding variables (age, ethnicity) for both sexes. Sleepiness has been linked to motor vehicle crashes in multiple observational studies. A cross-sectional study of 913 employed adults from the general U.S. population (enrolled in the Wisconsin Sleep Cohort Study) found that men and women with AHI >15 were significantly more likely to have multiple accidents over the past 5 years (OR, 7.3; 95% CI, 1.8 to >25; adjusted for age, miles driven, and sex) using state records for motor vehicle accident history (retrospectively). The study was limited by the retrospective design and potential confounding. Considering education and usual alcohol consumption reportedly did not alter the odds ratio. None of their measures of perceived sleepiness (including those derived from ESS) were significantly related to accident occurrence. A cross-sectional study of 2,342 Australian commercial vehicle drivers found that the sleepiest five percent of drivers (based on ESS) had about twice the odds of a self-reported motor vehicle accident over the previous three years (OR, 1.91; 95% CI, 1.09 to 3.35) and even greater odds of multiple accidents over the previous three years (OR, 2.67; 95% CI, 1.29 to 5.52).

   Note that the various studies reporting associations between sleepiness and health outcomes do not establish the degree to which a reduction in sleepiness would result in improved health outcomes (and they are not all limited to people with OSA).

4. Is there an association between reduction in blood pressure and health outcomes?

   CQ 4 is addressed in the first paragraph under "Benefits and Harms of Treatment for OSA" (pg 35-36). Briefly, yes, data suggest that mean reductions of 2 to 3 mm Hg for systolic

blood pressure (across a population) could result in a clinically significant reduction in cardiovascular mortality (by 4% to 5% for coronary heart disease and 6% to 8% for stroke).

5. What are clinically meaningful changes in the AHI, sleepiness (as measured by the Epworth Sleepiness Scale), and blood pressure?

   There is no clear numerical change in AHI that constitutes a clinically meaningful change for AHI. Reducing it from severe OSA levels to normal (<5) or near normal levels could possibly be clinically meaningful. Our KQ 6 findings suggest that it may be clinically meaningful, but empiric data to confirm that is lacking.

   CQ 5 is addressed also in the first paragraph under "Benefits and Harms of Treatment for OSA" (pg 35-36). Briefly, for sleepiness, the threshold for a clinically significant change in ESS is somewhat uncertain. Although a reduction from ESS ≥10 (indicating excessive daytime sleepiness) to one of <10 (considered the normal range) is likely clinically meaningful, recent systematic reviews found that some experts consider a 1 point change in ESS clinically significant. However, other sources suggest that a greater change, of at least 3 or 4 points, should be the clinically significant threshold. For example, some trials that use ESS as an outcome have considered a ≥ 4-point change in ESS as clinically significant for their sample size calculations or in their interpretation of findings.[242-244] Also, the American College of Chest Physicians' outcome experts evaluating the ESS informally stated that a clinically significant change in the ESS is probably at least ≥3; a specific example cited was that a reduction by 1 point (e.g., from 3 [high] to 2 [moderate]) on two out of seven ESS domains was unlikely clinically relevant.

   For blood pressure reduction, some authors suggest that a difference of more than 9/10 mm Hg is clinically meaningful for individuals. However, across a population, guidelines have suggested that much smaller reductions of 2 to 3 mm Hg for systolic blood pressure could result in a clinically significant reduction in cardiovascular mortality (by 4% to 5% for coronary heart disease and 6% to 8% for stroke).

6. Is there an association between OSA and incident diabetes?

   CQ 6 is addressed in the Limitations section of the report when mentioning that we did not evaluate the association between AHI and incident diabetes (pg 38). A 2011 systematic review concluded that there may be an association but the strength of evidence was low and the association may be confounded by obesity. A more recent (2014) systematic review concluded that the association between OSA and incident diabetes is uncertain.