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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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Structured Abstract

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

Data Sources: PubMed/MEDLINE, the Cochrane Library, Embase, and trial registries through August 23, 2021; reference lists of retrieved articles; outside experts; and reviewers, with surveillance of the literature through September 23, 2022.

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 reporting on health outcomes, studies evaluating accuracy of screening questionnaires or clinical prediction tools in asymptomatic adults with OSA or persons with unrecognized symptoms of OSA, and systematic reviews of treatment reporting on changes in blood pressure (BP) and apnea-hypopnea index (AHI) scores.

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

Data Synthesis: No reviewed RCT directly compared screening with no screening. In two studies (702 total participants), the screening accuracy measured as AUC of the Multivariable Apnea Prediction (MVAP) score followed by unattended home sleep testing for detecting severe OSA syndrome (AHI ≥30 and Epworth Sleepiness Scale [ESS] score >10) was 0.80 (95% confidence interval [CI], 0.78 to 0.82) and 0.83 (95% CI, 0.77 to 0.90), respectively. Studies evaluating the Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference, Gender (STOP-BANG) Questionnaire (k=4) and the Berlin Questionnaire (BQ) (k=2) enrolled different populations and used different criteria for a positive screening test. Recent systematic reviews of positive airway pressure (PAP) and mandibular advancement devices (MADs) show an association between PAP and MAD and reduction in BP and AHI, however reduction in BP outcomes versus inactive control is relatively small (2 to 3 mm Hg). Meta-analysis found that PAP compared with any control was associated with a significantly larger reduction in ESS score change (pooled mean difference, -2.33 [95% CI, -2.75 to -1.90]; 47 trials, 7,024 participants), modest improvement in sleep-related quality of life (QOL) (standardized mean difference, 0.30 [95% CI, 0.19 to 0.42]; 18 trials, 3,083 participants), and improved general health-related QOL measured by the SF-36 mental health component summary score change (2.20 [95% CI, 0.95 to 3.44]; 15 trials, 2,345 participants) and SF-36 physical health component summary score change (pooled mean difference, 1.53 [95% CI, 0.29 to 2.77]; 13 trials, 2,031 participants). Meta-analysis also found that use of MADs was associated with a significantly larger ESS score change than controls (pooled mean difference, -1.67 [95% CI, -2.09 to -1.25]; 10 trials, 1,540 participants). Reporting of other health outcomes was sparse; no included trial found significant benefit associated with PAP or MAD on mortality, cardiovascular outcomes, stroke, or motor vehicle accidents. Common adverse effects of PAP and MADs included oral or nasal dryness, irritation, and pain, among others.

Limitations: Two studies assessing the accuracy of the MVAP score oversampled participants at high risk of OSA and those with OSA syndrome. No study prospectively evaluated screening

tools to report calibration or clinical utility for improving health outcomes. Three studies assessing the accuracy of the STOP-BANG and two assessing the BQ enrolled different populations and used different criteria for positive screening tests. Most included trials assessing the benefit of PAP and MADs reported outcomes over a relatively short duration (12 weeks or less), and most pooled estimates showing improvement in excessive sleepiness or QOL (except benefit of PAP for improving ESS scores) fell short of the range considered to be a minimal clinically important difference. Populations enrolled in trials of treatment were referred for treatment; no trial enrolled populations who were identified by screening in primary care.

Conclusions: The accuracy and clinical utility of potential screening tools for OSA that could be used in primary care settings are uncertain. PAP and MADs reduce AHI, BP and ESS score. Trials of PAP have not established whether treatment reduces mortality or improves most other health outcomes, except for its modest improvement in sleep-related QOL and general health–related QOL.

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Chapter 1. Introduction

Scope and Purpose

The United States Preventive Services Task Force (USPSTF) will use this review to update its recommendation on screening for obstructive sleep apnea (OSA) in adults. In 2017, the USPSTF concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for OSA in asymptomatic adults (I statement).[1]

Condition Definition

OSA is a sleep disorder characterized by episodes of narrowing and obstruction of the pharyngeal airway during sleep resulting in reductions or cessations in breathing.[2] By definition, OSA consists of more than five events per hour of partial or total upper airway obstruction despite efforts to breathe.[3] Total airway obstruction (>90%) for more than 10 seconds is defined as apnea, whereas hypopnea is a partial airway obstruction (>30%) with at least a 3 percent reduction in oxyhemoglobin saturation or sleep arousals.[4] The apnea-hypopnea index (AHI) is used to define the severity of OSA. The AHI categorization cutoffs vary slightly depending on the source but are similar to cutoffs proposed by Veasey and Rosen:[4] mild OSA—5 to 15 events per hour; moderate OSA—16 to 30 events per hour; and severe OSA—more than 30 events per hour. Common clinical signs and symptoms of OSA include excessive daytime sleepiness (EDS), unrefreshing sleep despite length of sleep, loud or irregular snoring, and choking or gasping at night.[5] The *International Classification of Sleep Disorders, Third Edition* includes both physiological measurements and clinical signs and symptoms in its OSA definition: a respiratory disturbance index (RDI) of five or more events per hour as determined by polysomnography (PSG) in addition to the common clinical symptoms of OSA or an RDI of 15 or more events per hour with or without clinical symptoms.[6] The RDI includes the number of respiratory effort–related arousals per hour in addition to the number of apnea and hypopnea events.[7]

Etiology and Natural History

OSA is caused by a narrowing of the upper airway leading to either a reduction or cessation of airflow during sleep. Although anatomical abnormalities are implicated in OSA, evidence suggests there are multifactorial causes.[2, 8] A common cause for the restriction in the upper airway is obesity, which may include adipose tissue in areas around the airway, increased lingual fat, and abdominal fat leading to reduced lung volume.[9] Other causes leading to a narrow pharyngeal airway are enlarged tonsils;[10] an anatomically long upper airway, particularly in men;[9] and a small craniofacial structure, especially in Asian populations.[11, 12] The conclusions of one systematic review (SR) and meta-analysis[8] that compared craniofacial and upper airway morphology of patients with OSA with those of controls indicated that patients with OSA displayed a reduced pharyngeal airway space, a greater total anterior facial height, and an inferior position of the hyoid bone. Nonanatomic contributions included reduced upper airway

dilator muscle control and functions that are responsible for neural control, reduced muscle responsiveness, and reduced muscle effectiveness; an unstable or overly sensitive respiratory control system; and a low respiratory arousal threshold that leads persons to wake up too easily when airways narrow which possibly reduces pharyngeal muscle activity.[2, 9] In recent years, research has focused on metabolic disease as a contributing factor to OSA, specifically insulin resistance and leptin deficiency and possibly glycemic control;[13] however, further research may be warranted to identify the mechanisms involved and the direction of the association between OSA and metabolic disease.

Left untreated, OSA is associated with multiple adverse health outcomes. However, the natural history of OSA progression rates (from mild to severe) is unclear. For example, the extent to which mild, asymptomatic OSA progresses in severity independent of other factors such as weight gain is unclear and not well described in the current literature. Some researchers have examined multiple complications of OSA and have hypothesized comprehensive models that have accounted for the relationships between OSA and adverse health outcomes. For instance, some researchers suggested that metabolic factors both influence the development of OSA and are products of OSA, in which visceral obesity is the common etiological factor.[13, 14]

Risk Factors

Risk factors for OSA include male sex (odds ratio [OR], 3.1 [95% confidence interval {CI}, 2.5 to 3.8]), 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).[15-31]

Persons with OSA (especially moderate to severe OSA) have an increased incidence of hypertension (HTN), which may be a risk factor for OSA as well as an adverse health consequence of untreated OSA. However, the presence of HTN alone is not useful in detecting persons at increased risk of OSA.[21] Smoking, alcohol use, sedative use, and nasal obstruction (e.g., due to nasal congestion) have been suspected of increasing OSA risk, but these factors are supported by sparse or mixed evidence.[21, 32-39]

Prevalence and Burden

Prevalence

The prevalence of OSA in the literature varies, in part, by the definition of hypopnea used for the study.[40] Older studies set higher AHI thresholds compared with more recent studies, making comparisons challenging.[21] Further, estimates may vary because of sampling biases, year of publication, or a combination of factors.[41] As noted in this section, the estimated prevalence of OSA in the U.S. population has increased in the past few decades, which primarily is attributed to the increased prevalence of obesity.[42] In addition, between 1999 and 2010, diagnoses of OSA in the National Ambulatory Medical Care Survey rose by 442 percent.[43]

Based on data from the Wisconsin Sleep Cohort Study (WSCS) and the 2012 National Health and Nutrition Examination Survey, estimated prevalence of any OSA (AHI ≥ 5) was 26 percent, and prevalence of moderate to severe OSA (AHI ≥ 15) was 10 percent.[42] A recent modeling study conducted in 2019 indicates that this is an underestimate of the prevalence that would be expected when using the most recent (2012) American Academy of Sleep Medicine scoring criteria to identify OSA; standardized prevalence using 2012 scoring criteria in the U.S. estimates were 33.2 percent for any OSA (AHI ≥5) and 14.5 percent for moderate to severe OSA (AHI ≥15).[44] Evidence about the prevalence of severe OSA (AHI ≥30) is scant, although clearly this prevalence would be lower than the combined prevalence of moderate to severe OSA.

Subpopulations

The prevalence of OSA appears to increase with age through the sixth to seventh decades and then plateaus.[16, 17, 31] 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.[16, 17, 28, 45] Based on data extrapolated from the WSCS and the 2012 National Health and Nutrition Examination Survey, the prevalence of moderate to severe OSA (AHI ≥15) among adults ages 30 to 70 years was 13 percent for men and 6 percent for women.[42] Using a standard definition of daytime sleepiness and an AHI of 5 or greater to define OSA, prevalence was 14 percent among men and 5 percent among women.[42]

A higher BMI is associated with an increased prevalence of sleep-disordered breathing, and the prevalence of OSA appears to be rising with the obesity rates in the United States.[23, 42] For instance, in men ages 30 to 49 years the prevalence of moderate to severe sleep-disordered breathing (AHI ≥15) was 55.0 percent in those with a BMI greater than or equal to 40, 16.6 percent with a BMI of 30 to 39.9, and 3.8 percent with a BMI of 25 to 29.9. In women ages 30 to 49 years, the prevalence of moderate to severe sleep-disordered breathing was 18.6 percent in those with a BMI greater than or equal to 40, 3.6 percent with a BMI of 30 to 39.9, and 0.73 percent with a BMI of 25 to 29.9.[42]

African American, Native American, and Hispanic populations have a higher prevalence of OSA compared with Whites; however, some evidence suggests that differences are partially explained by higher rates of obesity, asthma, and tobacco use among certain ethnic groups.[46]

Burden of Disease

Many adverse health outcomes have been associated with OSA in observational studies, primarily attributed to chronic disturbances in gas exchange (e.g., hypercapnia and hypoxemia), sympathetic nervous system arousal (e.g., oxidative stress caused by intermittent hypoxemia leading to sympathetic activation, cortical arousal independent of oxygen), and fragmented sleep. Untreated, severe OSA (AHI ≥30) is associated with increased all-cause mortality.[47, 48] However, there is controversy in the literature regarding the extent to which OSA independently contributes to various adverse outcomes (i.e., without the contributions of age, BMI, and other potential confounders). For example, OSA is associated with several cardiovascular (CV) risk factors, making it more difficult to establish an independent association between OSA and CV disease (CVD).

Specific adverse health outcomes associated with untreated OSA include increased higher rates of motor vehicle and other accidents,[48-55] cognitive impairment,[29, 56-58] lost work days,[59] work disability,[60] impaired work performance,[61] and decreased quality of life (QOL).[62] In addition, bidirectional associations between OSA and the following outcomes have been reported: CV events,[63, 64] coronary heart disease (CHD) and heart failure,[65-70] angina,[71, 72] atrial fibrillation,[73] stroke,[65, 74, 75] HTN,[23, 24, 76-80] and type 2 diabetes (DM2) and metabolic syndrome.[14, 81-84]

Subpopulations

Despite a lower prevalence of OSA, women may present with more OSA comorbidities, including insomnia, mood disorders, anxiety, and morning headache.[85]

Some evidence suggests that morbidity associated with OSA varies by symptom subtypes, particularly those experiencing EDS. For example, a 2019 cohort study (n=1,207 participants with at least moderate OSA) found a higher risk of incident heart failure, CHD, and CVD among those reporting excessive sleepiness compared with other subtypes (disturbed sleep, minimally symptomatic, and moderately sleepy).[86] A qualitative analysis (n=42) of U.S. patients with OSA and EDS concluded that EDS adversely affected multiple health-related QOL domains in the majority of participants, including physical health and functioning, cognition, relationships, emotions, and work productivity.[87]

Rationale for Screening and Screening Strategies

In theory, screening to identify unrecognized OSA followed by appropriate treatment could improve sleep quality, eliminate apneas and hypopneas, and normalize oxygen saturation levels to reduce risk of future adverse health outcomes. Potential screening strategies include formal screening questionnaires and clinical prediction tools in addition to combined screening approaches, which may use a questionnaire or clinical prediction tool followed by home-based oximetry testing for persons who score above a defined threshold on the questionnaire or clinical prediction tool. For persons who screen positive, a diagnostic test would be used to determine whether they have OSA (i.e., formal PSG in a sleep facility or unattended home sleep testing [HST] with a portable monitor [PM]).

The available screening questionnaires and clinical prediction tools attempt to identify persons at higher risk of OSA. Many of them combine questions about objective findings (e.g., BMI, neck circumference) with questions about symptoms associated with OSA. Screening questionnaires that could be considered for use in primary care include the STOP (Snoring, Tiredness, Observed apnea, blood Pressure) Questionnaire,[88] STOP-BANG Questionnaire (STOP Questionnaire plus BMI, Age, Neck circumference, and Gender),[89] the Berlin Questionnaire (BQ),[90] the Wisconsin Sleep Questionnaire,[28] and the Epworth Sleepiness Scale (ESS).[91] 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 or were limited by risk of spectrum bias, and also found that the accuracy and reliability in general primary care settings were unclear and may have been substantially overestimated.[21, 92]

The traditional confirmatory diagnostic test for OSA is a technologist-attended PSG conducted in a sleep laboratory facility. The use of PSG for diagnosis requires measurement of the following: electroencephalogram (EEG), electrooculogram, chin electromyelogram, airflow, oxygen saturation, respiratory effort, and electrocardiogram or heart rate.[93] Additional recommended measurements include body position and leg movements.[93] The frequency of events is typically reported as an AHI. In-laboratory PSG is costly and potentially inconvenient for patients. In-home PMs have been proposed as an alternative.[94] Sleep study monitors are generally classified into one of four types based on the signals recorded (**Appendix A Table 1**): type I is a facility-based PSG; the other types are PMs. The American Academy of Sleep Medicine (AASM) recommends using PSG or a home sleep apnea test with a technically adequate device to diagnosis OSA in uncomplicated adults presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA.[6] If the home testing result is negative, inconclusive, or technically inadequate, then PSG is recommended to ascertain diagnosis.[6] For patients with significant cardiorespiratory disease, potential respiratory muscle weakness, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid use, history of stroke, or severe insomnia, the AASM recommends using PSG rather than home testing for diagnosis.[6]

Treatment Approaches

Positive airway pressure (PAP) is the main treatment for OSA.[95, 96] PAP devices deliver compressed air into the airway and aim to maintain an open airway. These devices can deliver continuous PAP (CPAP), auto-adjusting PAP (APAP), or bilevel PAP (BPAP).[95] OSA treatment guidelines are summarized in **Appendix A Table 2**. The American College of Physicians recommends (1) to encourage all patients who are overweight or obese with OSA to lose weight (strong recommendation, low-quality evidence), (2) PAP as initial therapy for patients diagnosed with OSA (strong recommendation, moderate-quality evidence), and (3) mandibular advancement devices (MADs) as an alternative therapy to PAP for patients with OSA who prefer them or for those with adverse effects associated with PAP (weak recommendation, low-quality evidence).[96] In 2019, the AASM recommended that clinicians and patients discuss using CPAP or APAP (over BPAP) to treat OSA in adults with EDS, impaired sleep–related QOL, or comorbid HTN.[95] The AASM also recommends that PAP therapy be initiated using either APAP at home or in-laboratory PAP titration in adults with OSA and no significant comorbidity, noting that the choice of treatment delivery at home versus in a laboratory should be based on access, cost-effectiveness, patient preference, clinician judgment, and other factors.[95] This recommendation is qualified as being for persons with no significant comorbidities because it was based on studies that excluded patients with, for example, congestive heart failure, chronic opiate use, significant lung disease, neuromuscular disease, or history of uvulopalatopharyngoplasty (UPPP).[95] For patients who do not accept PAP treatment, AASM guidelines suggest that providers discuss alternative treatment options with patients, such as weight loss, positional therapy, oral appliance therapy, or surgical interventions. Other relevant AASM treatment guidelines are outlined in **Appendix A Table 2**.

Surgical interventions for OSA are available, but they generally are not considered first-line treatment options. PAP is by far the most commonly used treatment, and surveys of practice

patterns indicate that surgical treatments are rarely used.[97, 98] For example, the recently published AASM clinical practice guideline recommends that clinicians discuss referral to a sleep surgeon with adults with OSA and a BMI less than 40 kg/m^2 who are intolerant of PAP.[99] Types of surgical procedures that have been studied or used for OSA include the following: nasal and nasopharyngeal, oral and oropharyngeal, hypopharyngeal and laryngeal, global airway, upper airway bypass procedures, and implantable hypoglossal nerve stimulator. Specific procedures include UPPP, in which tissue is removed from the throat and from the rear of the mouth; maxillomandibular advancement, in which the jaw is surgically moved forward; soft palate implants; nasal polyp removal; tonsillectomy; and tracheostomy.

Clinical Practice in the United States and Recommendations of Other Organizations

The current frequency of routine screening for OSA in primary care and use of questionnaires to assess risk for OSA among those presenting with sleep-related symptoms is unclear. However, one 2011 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 clinicians.[100] Currently, most primary care clinicians refer patients with suspected OSA to a specialist to determine the appropriate diagnostic test and treatment, likely due to the complexity associated with diagnosis and with treatment selection.[101] Clinical practice guidelines related to screening and diagnosis of OSA are summarized in **Appendix A Table 3**. Most groups do not recommend routine screening in primary care settings among populations without signs or symptoms of OSA. One group (the AASM) recommends routine screening using a standardized questionnaire in groups considered high-risk for OSA, including those who are preoperative for bariatric surgery or who have any of the following conditions: obesity (BMI ≥30 kg/m^2), congestive heart failure, atrial fibrillation, treatment-resistant hypertension, impaired glucose tolerance or DM2, nocturnal dysrhythmias, stroke, pulmonary hypertension, and coronary artery disease.[102] Recent (2019) U.S. Department of Veterans Affairs (VA) guidelines suggest using the STOP Questionnaire to stratify the risk of OSA among patients who report sleep complaints (graded as a weak recommendation by the VA guideline work group) and also suggest assessing for sleep-disordered breathing in patients with a history of CV or cerebrovascular events, congestive heart failure, and chronic opioid use[103] (graded as a weak recommendation by the VA guideline work group).

Chapter 2. Methods

Key Questions and Analytic Framework

The scope of work and key questions (KQs) were developed by the Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers. The analytic framework and KQs that guided the review are shown in **Figure 1**. Six KQs were developed for this review:

1. Does screening for obstructive sleep apnea (OSA) in adults improve health outcomes, including for specific subgroups of interest?
2. What is the accuracy of screening questionnaires, clinical prediction tools, and multistep screening approaches (e.g., using a questionnaire followed by home-based oximetry/testing) in identifying persons in the general population who are more or less likely to have OSA, including for specific subgroups of interest?
3. What are the harms associated with screening or subsequent diagnostic testing for OSA, including for specific subgroups of interest?
4. How effective is treatment with positive airway pressure (PAP) or mandibular advancement devices (MADs) for improving intermediate outcomes (i.e., the apnea-hypopnea index [AHI] or blood pressure) in persons with OSA, including for specific subgroups of interest?
5. How effective is treatment with PAP or MADs for improving health outcomes in persons with OSA, including for specific subgroups of interest?
6. What are the harms associated with treatment of OSA using PAP or MADs, including for specific subgroups of interest?

In addition to addressing the KQs, this review also looked for evidence related to two contextual questions (CQs) that focused on (1) barriers to undergoing diagnostic testing for OSA and (2) the association between AHI and health outcomes. These CQs were not a part of this systematic review but are intended to provide additional background information. Literature addressing the CQs is summarized in **Appendix A**.

Data Sources and Searches

PubMed/MEDLINE, the Cochrane Library, and Embase were searched for English-language articles published through August 23, 2021. Medical Subject Headings were used as search terms when available and keywords when appropriate, the search focused on terms to describe relevant populations, tests, interventions, outcomes, and study designs. Complete search terms and limits are listed in **Appendix B**. Targeted searches for unpublished literature were conducted via ClinicalTrials.gov. To supplement electronic searches, the reference lists of pertinent review articles and studies that met the inclusion criteria were reviewed. Studies suggested by peer reviewers or public comment respondents were reviewed and, if appropriate, incorporated into the final review. Since August 23, 2021, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that

may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on September 23, 2022, and no additional studies meeting eligibility criteria were identified. All literature search results were managed using EndNote™ version 9.2 (Thomson Reuters, New York, NY).

Study Selection

Inclusion and exclusion criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs were developed with input from the USPSTF (**Appendix B**). We included English-language studies of adults ages 18 years or older conducted in countries categorized as "very high" on the Human Development Index.[104] We excluded studies of children, adolescents, pregnant women, and adults with central sleep apnea or acute stroke or other acute conditions that can trigger onset of OSA. We also excluded studies focused on the screening, diagnosis, or treatment of OSA among persons with rare conditions (e.g., acromegaly) for whom testing (rather than screening and primary prevention) for OSA is considered part of standard disease management. Studies focused on screening in occupational settings (e.g., during a workplace fitness-for-duty evaluation) were also excluded.

For KQs 1 and 3 (direct evidence of benefits and harms of screening, respectively), and KQ 2 (accuracy of clinical prediction tools or screening questionnaires), we included studies that enrolled asymptomatic adults with OSA or persons with unrecognized symptoms of OSA; those that enrolled referral populations were not eligible. For KQ 1, RCTs comparing screened with nonscreened groups reporting on health outcomes were eligible. For KQ 2, prospective cohort studies and cross-sectional studies that evaluated the accuracy of screening questionnaires or clinical prediction tools (alone or followed by an unattended HST) 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. For KQ 2, we excluded studies limited to persons who were referred to sleep laboratories for suspected OSA and excluded studies where only a subgroup (usually the highest risk group) had PSG because of concern for verification bias. For KQ 3 (harms of screening), we included studies eligible for KQ 1 or KQ 2 that reported harms of screening or diagnostic tests, such as false-positive results leading to unnecessary treatment, anxiety, condition-specific distress, or stigma.

For KQs 4 through 6 (benefits and harms of treatment), we included studies evaluating PAP or MADs compared to an inactive control; other interventions were not eligible (e.g., oropharyngeal exercises, weight loss interventions). For KQ 4 (benefit of treatment for improving intermediate outcomes), we limited inclusion to good-quality, recent (within 5 years) SRs comparing PAP or MADs with an inactive control that reported on changes in BP outcomes or in AHI. For KQs on the benefit of treatment for improving health outcomes (KQ 5) and harms of treatment (KQ 6), RCTs of asymptomatic adults with OSA and/or symptomatic adults with a confirmed diagnosis of OSA were eligible.

Titles and abstracts were independently reviewed by two investigators; those marked for potential inclusion by either reviewer were retrieved for evaluation of the full text. The full texts

were then independently reviewed by two investigators to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

Quality Assessment and Data Abstraction

Two investigators independently assessed the quality of the included studies by using criteria defined by the USPSTF adapted for this topic and supplemented it with criteria from the Quality Assessment of Diagnostic Accuracy 2 (QUADAS-2)[105] for diagnostic accuracy studies and from A Measurement Tool to Assess Systematic Reviews (AMSTAR) for SRs[106] (**Appendix B**). Each study was assigned a final quality rating of good, fair, or poor; disagreements were resolved by discussion and consensus. Only studies rated as having good or fair quality were included.

For each included study, one investigator extracted pertinent information about the methods, enrolled populations, interventions, comparators, eligible outcomes, timing, settings, and study designs. All data extractions were checked by a second investigator for completeness and accuracy.

Data Synthesis and Analysis

We qualitatively synthesized the findings for each KQ by summarizing the characteristics and results of included studies in tabular and narrative format. Summary tables and figures of study characteristics, population characteristics, intervention characteristics, and outcomes were used to assess the consistency, precision, and relationship of effect size with key potential modifiers. To determine whether meta-analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies following established guidance.[107] We had a sufficient number of similar trials to conduct a meta-analysis of studies examining the benefits of PAP and MAD. We ran random-effects restricted maximum likelihood models on continuous measures of sleepiness, general health–related QOL and sleep-related QOL when at least three similar studies were available. We calculated pooled estimates of the difference in mean change from the baseline score between the intervention and control groups; when studies reported on similar outcomes using multiple scales, we used the standardized mean difference (SMD) in change from the baseline score in pooled estimates. The meta command in Stata version 16 were used to conduct all quantitative analyses.[108] For our meta-analyses of PAP and MAD treatments, we stratified analyses by comparison groups, providing pooled estimates for studies using sham controls (e.g., a sham PAP 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 and by other factors when possible, including OSA severity and baseline sleepiness (ESS score).

For all quantitative analyses, the I^2 statistic was calculated to assess the statistical heterogeneity in effects between studies.[109, 110] An I^2 from 0 to 40 percent may not be important, an I^2 from 30 to 60 percent may represent moderate heterogeneity, an I^2 from 50 to 90 percent may represent substantial heterogeneity, and an I^2 of 75 percent or greater represents considerable heterogeneity.[111]

Expert Review and Public Comment

A draft research plan for this topic was posted on the USPSTF website for public comment from December 17, 2020, to January 20, 2021. In response to public comments, the treatment eligibility criteria were revised to clarify the variations of PAP that were eligible and that studies focused on screening specific occupational groups in the context of an occupational health examination for fitness for duty are excluded. The USPSTF made no substantive change that altered the scope of the review. The final version of the research plan was posted on the USPSTF website on March 4, 2021. The draft evidence review was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and addressed in revisions of this evidence review where appropriate. Revisions included clarifying in the Introduction and Methods that combined screening approaches for OSA were eligible (e.g., screening questionnaire followed by home-based oximetry testing for persons who score above a defined threshold on the questionnaire) and elaborating on the limitations of the current body of evidence in the Discussion. The draft evidence review was posted for public comment from March 29, 2022, through April 25, 2022. Revisions included clarifying current AASM clinical practice guidelines relevant to OSA in the Introduction and clarifying in the Introduction and Methods that the scope of the review does not include screening for OSA in occupational settings.

USPSTF and AHRQ Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and KQs and to resolve issues related to the scope for the final evidence synthesis.

AHRQ staff provided oversight for the project, coordinated systematic review, reviewed the draft report, and assisted in an external review of the draft evidence synthesis.

Chapter 3. Results

Literature Search

We identified 6,288 unique records and assessed 1,086 full-text articles for eligibility (**Figure 2**). We excluded 985 studies for various reasons, detailed in **Appendix C**, and included 86 studies reported in 101 articles. Of these, 26 studies (reported in 31 articles) and 2 companion articles to previously included studies are new and were not included in the previous USPSTF review on this topic. Details of quality assessments of included studies are in **Appendix D Tables 1–7**.

Results by KQ

KQ 1. Does Screening for OSA in Adults Improve Health Outcomes, Including for Specific Subgroups of Interest?

We found no eligible study that addressed this question.

KQ 2. What Is the Accuracy of Screening Questionnaires, Clinical Prediction Tools, and Multistep Screening Approaches (e.g., Using a Questionnaire Followed by Home-Based Oximetry/Testing) in Identifying Persons in the General Population Who Are More or Less Likely to Have OSA, Including for Specific Subgroups of Interest?

We included seven fair-quality studies[112-118] assessing clinical prediction tools or screening questionnaires compared with facility-based PSG, four of which were new to this review (**Table 1**).[115-118] Two evaluated the BQ,[112, 115] four evaluated the STOP-BANG Questionnaire[115-118] and two evaluated the Multivariable Apnea Prediction (MVAP) score—alone and when followed by an unattended HST.[113, 114] We found no eligible studies of good or fair quality evaluating other clinical prediction tools or screening questionnaires, such as the ESS.

BQ

The BQ classifies risk of OSA as high or low by using three categories related to snoring, tiredness, and BP (at least two positive categories constitute high risk).[90] In addition to the 10 questions, it also gathers information on age, sex, height, and weight. One of the two included studies evaluating the BQ randomly sampled Norwegians from the National Population Register to complete the Norwegian translation of the BQ (55% response rate).[112] Of those completing the questionnaire, 24 percent were classified as high risk and 518 had received in-hospital PSG. Of the 518 included in the analysis, 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), the authors' analyses adjusted for bias in the sampling procedure to report estimated screening properties for the general population. In

contrast, the second study[115] included a small (n=43) but unselected sample of adults with DM2 recruited from a U.S. general internal medicine clinic. A majority (53%) were female, the mean BMI was 38.3 kg/m^2, and the mean AHI was 31.2; the mean age of participants was not reported. All participants received PSG in laboratory. Neither study assessing the BQ described the race or ethnicity of enrolled participants.

The study enrolling Norwegians found suboptimal screening accuracy, as follows:[112] for AHI ≥5: sensitivity was 37 percent and specificity was 84 percent; for AHI ≥15, sensitivity and specificity were 43 and 80 percent, respectively (**Table 2**). Of note, because it has implications for the validity of studies that oversample high-risk groups (and illustrates the impact of spectrum bias), the studies' unadjusted analyses (reported only in online appendixes) show much higher sensitivity but lower specificity (for AHI ≥5: 79% and 41%, respectively; for AHI ≥15: 83% and 35%, respectively). The study enrolling participants with DM2 from a U.S. general medicine clinic assessed accuracy for mild (AHI 5–14), moderate (AHI 15-29), and severe OSA (AHI ≧30).[115] Specificity of the BQ was suboptimal for all categories of OSA (mild: 0%; moderate: 31%; severe: 26%). Sensitivity was higher for moderate OSA (89%) and for severe OSA (93%) but was lower for mild OSA (80%). Positive likelihood ratios (PLRs) ranged from minimal to small in both studies (PLRs: 0.83 to 2.5), indicating that an abnormal result on the BQ—at best—minimally increased the likelihood of OSA. The negative likelihood ratios (NLRs) also ranged from minimal to small, indicating that a normal BQ only minimally decreased the likelihood of OSA (NLRs: 0.24 to 0.8).

STOP-BANG Questionnaire

The STOP-BANG Questionnaire includes the following eight dichotomous items: snoring, tiredness, observed apnea, high BP, BMI, age, neck circumference, and gender (male).[88, 119] A score of less than 3 is considered low risk for OSA; a score of 3 or more represents moderate to high risk for OSA. Four studies assessed the accuracy of the STOP-BANG among diverse populations and used different scoring criteria as well as additional variables to determine a positive screen (**Table 1**).[115-118]

One study enrolled a small sample of adults (n=43) with DM2 recruited from a U.S. general internal medicine clinic.[115] A majority (53%) were female, the mean BMI was 38 kg/m^2, and the mean AHI was 31. All participants received PSG in a laboratory. This study used the established cut point for a positive test (3 or greater). A second study (n=91) enrolled participants with a recent diagnosis of mild to moderate Alzheimer's disease (AD) who were enrolled in a Spanish cohort study comparing cognitive progression among participants with OSA with those without OSA.[116] The median age was 76 years, 64 percent were female, the median BMI was 28 kg/m^2, the mean AHI was 21, and 57 percent had high BP. This study optimized the cutoffs for each item in the STOP-BANG and revised the criteria for a positive item for age (older than 70 years vs. older than 50 years), for BMI (>26 kg/m^2 vs. >35 kg/m^2), and for neck circumference (>26.5 cm vs. >40 cm), resulting in a modified STOP-BANG score.[116] A third study included Korean adults (n=1,033) who were part of a large, multiyear population-based cohort study. The mean age was 59 years, 48 percent were female, the mean BMI was 25 kg/m^2, and the mean AHI was 7.[117] In this study, the STOP-BANG was modified; sleepiness and neck circumference were eliminated, waist circumference and diabetes were included, and age had three cut points. The

investigators developed the modified score based on an exploratory sample (n=1,032) and examined accuracy in a validated sample of 1,033. A fourth study (n=199) included adults on opioids for chronic pain in a two-stage study.[118] Participants in the first stage of the study had a mean age of 52 years, were 58 percent female, had a mean BMI of 29 kg/m^2, and a median AHI of 6. In the first stage, the threshold for risk of OSA was either a STOP-BANG score greater than 3 or a resting daytime oxyhemoglobin saturation (SpO_2) of less than 95 percent. In the second stage, the 159 participants who met the threshold for risk received overnight oximetry at home, and those whose oxygen desaturation index was 5 or more were classified as at risk. No demographic data were provided for this subsample of 159 individuals. Because only a portion of the sample was included for the second stage, we did not include these accuracy data.

The study enrolling U.S. adults with DM2 found good sensitivity for detecting mild, moderate, and severe OSA (87%, 93%, and 94%, respectively), but very low specificity for the same subgroups (0%, 19%, and 15%, respectively) (**Table 2**).[115] In contrast, the study enrolling Spanish adults with AD found modest sensitivity and somewhat better specificity for severe OSA (61% and 76%, respectively).[116] PLRs and NLRs were minimal to small in both studies, indicating neither that a positive score on the STOP-BANG increased the risk of OSA nor that a normal score on the STOP-BANG decreased the risk of OSA. The study from Korea that included a general population of adults found moderate sensitivity and specificity for detecting all mild to moderate and severe OSA.[117] The study that included adults receiving opioids for chronic pain provided accuracy data for the STOP-BANG alone as well as accuracy for the STOP-BANG plus resting daytime SpO_2 (first stage). Sensitivity for the STOP-BANG to detect moderate to severe OSA was very good, but specificity was limited. Similarly, accuracy findings for the combination STOP-BANG plus resting daytime SpO_2 indicated excellent sensitivity but low specificity for all OSA as well as for moderate to severe and severe OSA. The NLRs for detecting all degrees of OSA and moderate to severe OSA were moderate (NLRs: 0.2), indicating that a normal screening modestly decreased the likelihood of any or moderate to severe OSA (NLRs: 0.2); the NLR for detecting severe OSA was large (NLR: infinity), indicating that a normal first-stage screening greatly decreased the likelihood of severe OSA.

MVAP Score

The MVAP score combines symptoms of snoring, choking, and witnessed apnea events with BMI, age, and sex.[120] It rates apnea risk between 0 and 1, with 0 representing the lowest risk and 1 representing the highest risk. Both included studies assessing the MVAP were conducted by the same research group from Philadelphia.[113, 114] One study evaluated Medicare recipients (n=452) from the city's greater metropolitan area, most of whom (74%) had daytime sleepiness.[113] The percentage with OSA was not reported, but 27 percent had OSA syndrome (OSAS), defined as the presence of OSA and excessive daytime sleepiness (AHI ≥5 and ESS >10). The second study evaluated patients with HTN from internal medicine practices at a Veterans Affairs Medical Center and a university-based HTN clinic (n=250).[114] Eighty percent of participants had OSA (AHI ≥5); of those, 22 percent had moderate OSA and 25 percent had severe OSA. Twenty-five percent of all participants had OSAS. The mean ages of participants were 71[113] and 53 years,[114] 60 to 64 percent were non-White, and the mean BMIs were 30 to 32 kg/m^2. The study of Medicare recipients included 70 percent women;[113] the other study included 20 percent women.[114] Key quality limitations included concern for attrition bias[114] and moderate

concern for selection bias or spectrum bias (with high prevalence of OSA, OSAS, and/or sleepiness among those receiving PSG; **Appendix D**).[113, 114]

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 2**). Sensitivity was 90[113] and 92 percent,[114] with specificity of 64 and 44 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 of less than 0.70 is thought to indicate inadequate discrimination.[121, 122] Calibration, which is often assessed by plotting the predicted risk versus the observed rate,[121] was not reported.

The study of patients with HTN also reported operating characteristics of MVAP to predict *any* OSAS (AHI ≥5 and ESS >10) using an MVAP cutoff score of 0.559. This study reported a sensitivity of 69.4 percent, a specificity of 56.5 percent, and an AUC of 0.614.[114]

MVAP Score Followed by HST

The same two studies described in the previous section also reported measures of discrimination for the MVAP score followed by unattended HST compared with in-laboratory PSG (**Table 1**).[113, 114] Both reported characteristics to predict *severe* OSAS (AHI ≥30 and ESS >10) using different HST AHI cutoffs: one used 15[113] and the other used 18.[114] Both studies found better operating characteristics with MVAP followed by an HST than with MVAP alone (sensitivity, 88% to 91%; specificity, 72% to 76%; AUC, 0.799 to 0.833).

The study of patients with HTN also reported operating characteristics of MVAP to predict *any* OSAS (AHI ≥5 and ESS >10) using an HST AHI cutoff of 13.5. It reported a sensitivity of 81 percent, a specificity of 54 percent, and an AUC of 0.672.

KQ 3. What Are the Harms Associated With Screening or Subsequent Diagnostic Testing for OSA, Including for Specific Subgroups of Interest?

We found no eligible study that addressed this question.

KQ 4. How Effective Is Treatment With PAP or MADs for Improving Intermediate Outcomes (i.e., AHI or Blood Pressure) in Persons With OSA, Including for Specific Subgroups of Interest?

We included four SRs of good quality comparing the intermediate outcomes of treatment with PAP or MAD (e.g., AHI, BP) versus those of control (**Appendix E Table 1**).[123-126] One limited inclusion to studies with oral appliances compared with an inactive control for improving BP outcomes and included 11 RCTs (based on searches of studies conducted through 2016); across all studies, follow-up duration ranged from 2 weeks to 4.65 years.[123] Two SRs limited to studies comparing PAP with an inactive control that reported on AHI and BP outcomes.[125, 126] One

limited inclusion to RCTs enrolling participants diagnosed with minimally symptomatic, asymptomatic, or nonsleepy OSA only and included fewer trials reporting on BP outcomes (k=7; 1,541 participants) than the second review, which had no limits on population criteria related to OSA severity and symptoms (k=23; 4,905 participants). One review was limited to populations with OSA and resistant hypertension (k=8; 606 participants).[124] Characteristics of studies included in each review (age, gender, BMI, and proportion of participants treated for HTN) are shown in **Appendix E Table 1**. Some reviews included a broader range of outcomes and trials and did not report characteristics separately for the subgroup of studies reporting on AHI or BP. All provided pooled estimates of AHI or BP outcomes, and all noted a high level of heterogeneity across trials in terms of duration, sample size, and population characteristics.

BP

MAD

One review found benefits associated with MAD compared to inactive control for improving BP; however, differences between groups were imprecise and not statistically significant.[123] Pooled estimates of mean change from baseline daytime systolic BP (SBP) among MAD versus control was -1.55 (95% CI, -4.65 to 4.25; 5 trials, 469 participants; I^2=0%), and -1.14 (95% CI, -2.78 to 3.38; 5 trials, 469 participants; I^2=0%) for daytime diastolic BP (DBP). Estimates for 24-hour BP were similar (**Appendix E Table 1**).

PAP

In the review limited to minimally symptomatic, asymptomatic, or nonsleepy populations, pooled data from five studies (1,541 participants) comparing CPAP to control demonstrated a small reduction in daytime DBP (-0.92 mm Hg [95% CI, -1.39 to -0.46]; I^2=0) and no significant difference between groups in daytime SBP (-0.51 mm Hg [95% CI, -3.39 to 2.38]; I^2=84%).[126] The second review of PAP included trials of any OSA severity and symptoms, and was conducted to support the AASM practice guidelines.[125] The scope of the review was broader than that of the outcomes related to AHI and BP. The task force for this review developed a clinical significance threshold between 1 and 2 mm Hg for BP change based on other commonly used thresholds in the literature, consensus after accounting for literature review, and clinical judgment.[125] Pooled analyses showed that PAP was associated with a reduction in a mean 24-hour BP of -2.63 mm Hg (95% CI, -3.86 to -1.39; 8 trials, 994 participants; I^2=0%). Pooled estimates for change in daytime SBP and DBP between groups were also significantly lower among PAP versus among control groups, ranging from -2.76 mm Hg to -1.98 mm Hg, respectively (**Appendix E Table 1**).

Two reviews focused on the effect of PAP in populations with hypertension and OSA. One review of PAP was limited to studies enrolling participants with resistant hypertension (k=23; 4,905 participants) as defined by the American Heart Association: uncontrolled range of BP despite the use of three antihypertensive medications, including a diuretic drug at the optimal dose, or controlled BP despite the use of four or more antihypertensive medications. Pooled analysis showed a reduction in mean 24-hour systolic BP (-5.06 mm Hg [95% CI -7.98 to 2.13]; I^2=84%) and mean 24-hour diastolic BP (-4.21 mm Hg [95% CI -6.50 to -1.93]; I^2=81%). PAP

was also associated with reductions in mean nighttime systolic and diastolic BP but not daytime systolic and diastolic BP (**Appendix E Table 1**).[124] The review for the AASM also reported on estimates among groups based on hypertensive status and severity; however, fewer studies were included in pooled estimates than the review described above. Estimates were similar in magnitude for participants with treatment-resistant HTN and for those who had received treatment for HTN (**Appendix E Table 1**). Pooled estimates from four trials (409 participants) with treatment-resistant HTN, defined as requiring three or more antihypertensive medications, demonstrated that PAP was associated with a reduction in a mean 24-hour BP of -2.06 mm Hg (95% CI, -4.12 to -0.00 mm Hg). Similarly, pooled estimates from four trials (627 participants) with treated HTN demonstrated a reduction in mean 24-hour BP of -2.16 mm Hg (95% CI, -3.59 to -0.72 mm Hg).[125]

AHI

Two reviews reported on the difference between groups in change from baseline AHI, and both reviews focused on PAP.[125, 126] The 2016 review to support the AASM practice guidelines found a greater reduction in AHI associated with PAP than with controls (pooled mean difference: -23.41 events per hour [95% CI, -28.51 to -18.30]; 11 trials, 832 participants).[125] The second review—which limited inclusion to studies of asymptomatic adults with OSA or those of minimally symptomatic, nonsleepy adults—included fewer studies (3 trials, 1,541 participants) and found a pooled mean difference of -15.57 events per hour (95% CI, -29.32 to -1.82).[126] Despite a difference in scope and in the number of included trials, the pooled estimates in AHI reduction favoring PAP were generally consistent. Both estimates were associated with heterogeneity (**Appendix E Table 1**). The review limited to asymptomatic, nonsleepy populations attributed heterogeneity to the results of a single study.[126, 127]

KQ 5. How Effective Is Treatment With PAP or MADs for Improving Health Outcomes in Persons With OSA, Including for Specific Subgroups of Interest?

We included 73 good- or fair-quality RCTs (reported in 87 articles) that reported at least one eligible health outcome. Characteristics and results are summarized in this section and are organized by treatment type.

PAP

Sixty-three RCTs (reported in 74 articles) comparing PAP with sham PAP (29 RCTs, 33 articles)[127-159] or another inactive control (34 RCTs, 41 articles)[160-200] 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. The majority of trials were conducted in a single country, including the United States (k=13),[130, 131, 135, 141, 144, 145, 149, 150, 173, 178, 189, 194, 196] Spain (k=16),[127-129, 133, 134, 148, 160, 162, 163, 165, 167, 180-182, 188, 192] the United Kingdom (k=15),[132, 138, 140, 151, 154-156, 158, 168-172, 183, 184, 195] Australia (k=5),[136, 147, 153, 164, 175] Hong Kong (k=4),[137, 177, 179, 197] and one each in Canada,[190] Denmark,[161] Norway,[199] and New Zealand.[146] Three trials enrolled participants from multiple country settings: one from Australia

and North America,[193] one from the United Kingdom and Canada,[166] and one from the United States and Canada.[157]

Most trials (k=53) followed participants for 12 weeks or less; 10 trials followed participants over a longer duration, including 16 to 24 weeks (k=5)[141, 166, 175, 193, 199] 52 weeks (k=3);[162, 184, 196] one did so for a median of 4 years;[163] and one for a median of 4.7 years.[185] The mean age of enrolled populations ranged from 44 to 78 years, and most trials enrolled populations with a mean age of 40 to 59 years; seven enrolled populations with a mean age of 65 years or older.[131, 149, 167, 181, 184, 185, 188] The vast majority of participants in most trials were males, with females comprising up to one-third of the enrolled population in 38 trials; one trial limited enrollment to females,[165] and three enrolled a majority of females.[192, 197, 201] Most trials did not describe race or ethnicity of enrolled populations, and those that did (k=14) used heterogeneous categories and varying levels of detail (**Appendix E Tables 2 and 3**). Five trials reported only on the proportion who were non-Caucasian, non-White, or non-European American (range: 5% to 40%).[131, 141, 150, 189, 195] One trial enrolled a majority of participants who were Black or biracial (52%),[130] seven trials enrolled fewer Black or African American participants (range: 5% to 20%),[135, 144, 157, 173, 193, 194, 196] and five trials enrolled some Asian participants (range: 2% to 8%).[135, 173, 184, 193, 194] Few trials reported on other categories of race or ethnicity. The mean BMI was 30 to 36 kg/m^2 in most trials (range: 25–47 kg/m^2). Two trials that enrolled participants with a mean BMI greater than 40 both limited participation to populations with OSA and obesity.[182, 192] The mean or median baseline AHI (or similar measure) was in the severe OSA range (AHI ≥30) for most trials; 13 trials reported mean baseline AHI in the moderate OSA range (AHI 16 to 30),[131, 146, 149, 154, 164, 168, 177, 184, 185, 193, 196, 197, 199] and six reported mean baseline AHI in the mild OSA range (AH1 5 to 15).[157, 166, 169, 171, 189, 195] The severity of OSA for participants enrolled in trials most frequently ranged from moderate to severe (k=29) or from mild to severe (k=16). Seventeen trials limited participants to more narrow ranges: mild only,[171, 195] mild to moderate or moderate only,[146, 157, 164, 185, 188, 189, 193] or severe only.[127, 147, 167, 179-182, 192] One trial did not report sufficient data to determine the range of OSA severity of participants.[166] Mean or median baseline ESS was 10 or greater in most trials, indicating EDS. Eighteen trials reported a mean baseline ESS of less than 10,[127, 131, 134, 154, 161-163, 166, 167, 173, 175, 180, 185, 188, 192, 196, 197, 199] and six trials did not report a baseline ESS.

Mortality

Thirty-one RCTs reported on mortality (**Appendix E Table 4**). The vast majority (28 RCTs) reported mortality rates at 12 weeks or less, and most of these (25 RCTs) reported no death in any study group;[127, 128, 133, 135, 138, 144, 146, 148-150, 154-157, 160, 164, 168-173, 177, 189, 190] three trials (536 total participants) reported one death, either in the PAP[166] or sham PAP group[134, 161] at 12 weeks. Three RCTs assessed mortality over a longer duration, and none found a statistically significant difference between groups. One (n=1,105) reported two deaths in each study arm over 24 weeks.[141] Two reported on mortality over a median duration of 4 to 5 years; one (n=723) reported eight deaths in the PAP group and three in the control group (incidence density ratio, 2.6 [95% CI, 0.70 to 11.8]; p=0.16),[163] and the second (n=364) found a similar number of deaths among the PAP and control groups (8% vs. 7%, respectively).[185]

General Health-Related QOL

Twenty-eight RCTs reported one or more measures of general health–related QOL. Twenty measured QOL using the Medical Outcome Short-Form (36-Item) Health Survey (SF-36).[127, 134, 138, 147, 148, 155-157, 164, 166, 171, 174, 177, 182, 184, 193, 195, 196, 199, 200] Most trials reported changes on the SF-36 physical component summary score (PCS) and the mental component summary score (MCS). Pooled analyzes in change from baseline SF-36 MCS found a statistically significantly greater improvement among the PAP group than among the control group (2.20 [95% CI, 0.95 to 3.44]; 15 trials, 2,345 participants).[127, 134, 138, 148, 155-157, 166, 174, 182, 193, 195, 196, 199, 200] Similarly, pooled analyses for change in SF-36 PCS from baseline found significantly greater improvement among the PAP group than among the control group (1.53 [95% CI, 0.29 to 2.77]; 13 trials, 2,031 participants) (**Table 3** and **Appendix F Figure 1**).[127, 134, 138, 148, 155-157, 174, 182, 195, 196, 199, 200] The pooled estimates for change from baseline SF-36 MCS and SF-36 PCS associated with PAP were smaller than the range considered a minimal clinically important difference (MCID), which is 4 to 7 for both SF-36 component summary scores.[202, 203] Two RCTs reporting on changes in total SF-36 scores at 12 weeks found inconsistent results; one (n=61) reported no difference between groups (but did not provide numerical data),[147] and one (n=179) found significantly greater improvement among the PAP group than among the control groups (mean change from baseline, 4.7 vs. 2.0; $p<0.05$).[164]

Eight RCTs measured general QOL using another tool, including the Nottingham Health Profile (k=4),[168-171] the EuroQol (k=3),[133, 166, 195] and the SF-12 (k=1)[165] (**Appendix E Table 4**). Overall, results were mixed. For the Nottingham Health Profile, three trials found no difference between groups in the change from baseline overall scores,[169-171] and one reported greater improvement in the PAP group compared with the control groups (4.9 vs. 7.9 [lower scores indicate greater improvement]; $p=0.002$).[168] In the three trials reporting on the EuroQol, two found no difference between groups in change from baseline score over 12 to 24 weeks,[166, 195] and one (n=340) only reported within-group changes; the PAP group improved at 12 weeks compared with baseline ($p<0.001$; effect size [standard deviation units], 0.38), but no improvement was seen in the control group.[133] Finally, one trial (n=307) reporting on changes in SF-12 at 12 weeks found a significantly greater improvement on the PCS among the PAP group versus the control group, but no difference on the MCS score.[165]

Sleep-Related QOL

Seventeen RCTs assessed sleep-related QOL—6 using the Sleep Apnea Quality of Life Index (SAQLI),[142, 155, 158, 166, 177, 184] 10 using the Functional Outcomes of Sleep Questionnaire (FOSQ),[127, 146, 148, 153, 157, 164, 172, 182, 195, 199] and 1 using the Quebec Sleep Questionnaire.[167] Our meta-analysis (combining all measures) found that PAP was associated with a small but statistically significant improvement in sleep-related QOL compared with controls (SMD, 0.30 [95% CI, 0.19 to 0.42]; 17 trials, 3,083 participants) (**Appendix F Figure 2**). Our subgroup analysis by mean baseline ESS found a similar but slightly larger effect size in trials with a mean ESS of 10 or greater (SMD, 0.35 [95% CI, 0.22 to 0.49]; 11 trials, 2,228 participants); in studies with a mean baseline ESS less than 10, the effect size was smaller and the pooled estimate was not statistically significant (**Appendix F Figure 4**). Results shown as a mean difference in scores for each sleep-related QOL measure are provided in **Appendix F Figure 3** and summarized in

Table 3. For both measures, the pooled mean difference falls below the range considered an MCID.

Cognitive Impairment

Fourteen RCTs reported one or more measures of cognitive function.[127, 141, 144, 146, 164, 167-171, 178, 181, 184, 188] No study reported on a global measure of cognition. Common measures included neurocognitive measures of verbal learning and memory, alertness, and reaction time. In general, studies assessed cognitive function using heterogeneous outcome measures and reported inconsistent results (**Appendix E Table 4**).

Motor Vehicle Accidents

Three RCTs reported on the incidence of motor vehicle accidents (MVAs), and none found a statistically significant difference between groups (**Appendix E Table 4**).[141, 173, 184] One trial (n=212) found no MVA at 12 weeks,[173] and two found similar rates among PAP and comparator groups at 24 weeks (10 vs. 11 MVAs out of 1,105 participants)[141] and 1 year (2 vs. 1 MVAs out of 278 participants).[184]

CV Events

Ten RCTs reported on the incidence of one or more CV events (**Appendix E Table 4**).[134, 141, 146, 158, 163, 166, 173, 184, 185, 199] Trials reported on heterogeneous categories of CV outcomes. Six trials (1,773 total participants) reported on the incidence of myocardial infarction (MI). In four of the six trials, a total of one MI occurred (combined) in either group (the control group) over 3 weeks to 1 year.[146, 166, 173, 184] Two trials reported on outcomes over a median of 4 to 5 years; one (n=723) reported two MIs in the PAP group and eight in the control group,[163] and the second (n=244) found a similar number of MIs in the PAP and control groups (9% vs. 7%, respectively).[185]

Five RCTs reported on the incidence of various other CV events (angina, unstable angina, and atrial fibrillation, pacemaker implantation due to syncope and prolonged pauses); trial durations were 12 weeks,[134, 173] 24 weeks,[166, 199] and 1 year.[184] Overall, too few events occurred to draw conclusions. Across four trials reporting on angina or unstable angina (570 total participants), four versus nine angina events occurred among the PAP versus comparator groups, respectively.[134, 166, 173, 184] For atrial fibrillation (k=3), one trial (n=212) reported a single case of incident atrial fibrillation at 12 weeks (randomized to the control group);[173] and in two trials assessing outcomes at 6 months and 1 year (669 total participants), there was no difference in the incidence of atrial fibrillation between the PAP and control groups (12 vs. 19 events).[166, 184] One trial limited to participants with atrial fibrillation (n=104) reported two cases of pacemaker implantation due to syncope or prolonged pauses among participants randomized to PAP over 24 weeks.[199]

One RCT reported one event in either group for each of the following events (**Appendix E Table 4**): incident heart failure,[163] unspecified tachyarrhythmia requiring hospitalization,[173] percutaneous coronary intervention for worsening angina,[173] and emergent cardiac surgery.[158]

One trial reported only an overall number of CV events (as adverse events) without describing how outcomes were measured or defined (31 vs. 29 events in PAP and control arms, respectively).[141] One trial reported hospitalizations for unstable angina or arrhythmia (17 vs. 11 in the PAP and control arms, respectively; 723 total participants).[163]

Cerebrovascular Events

Eight trials reported on the incidence of transient ischemic attacks[163, 166, 184] and/or strokes.[163, 166, 173, 184, 185, 195, 196, 199] Overall, too few events were observed to draw conclusions. In four studies measuring outcomes at 1 year or less, three found zero or one event in each group for transient ischemic attacks and strokes,[166, 173, 184, 195] and one reported two events in each arm[196] (**Appendix E Table 4**). Two trials measured outcomes over a median of 4 to 5 years.[163, 185] Both reported fewer events in the PAP group versus the control group; however, overall event rates were low and differences between groups was less than three events per group and were not statistically significant.

Headaches

In one RCT (n=37), three participants in the control group developed headaches at 4 weeks compared with none in the PAP group.[171]

ESS

Forty-seven RCTs reported sufficient ESS data to include in meta-analyses. Most were 12 weeks or less in duration; seven followed participants for 24 weeks,[141, 193, 199] 48 to 52 weeks,[162, 184, 196] or longer.[163] Our meta-analyses found that PAP reduced mean ESS scores more than controls (pooled mean difference: -2.33 [95% CI, -2.75 to -1.90]; 47 trials, 7,024 participants) (**Figure 3**). The pooled mean difference is within the range considered an MCID for the ESS (-2 to -3).[204, 205] Our analyses found substantial statistical heterogeneity that may be due to variation in PAP devices, participant characteristics (e.g., baseline ESS), treatment adherence, study duration, or chance; however, we were unable to find a clear explanation. As shown in **Figure 3**, heterogeneity is lower in subgroups defined by narrow ranges of OSA severity (severe only and mild or mild-moderate, vs. mild-severe) (**Figure 3**). However, the meta-analyses by OSA severity subgroup (4 categories: mild to severe, mild only and mild to moderate, moderate only and moderate to severe, and severe only) did not find a clear difference by OSA severity. Differences in mean score change were -2.61, -1.91, -2.21, and -3.08, respectively, and CIs overlapped; the analysis still found considerable statistical heterogeneity within the mild to severe, and moderate or moderate to severe groups (**Figure 3**). Four studies reporting on ESS did not provide sufficient data to be included in meta-analyses; however, results were consistent with the pooled estimates above.[131, 183, 194, 198]

Subpopulations

The Apnea Positive Pressure Long-term Efficacy Study found no significant overall difference in improvement of QOL between PAP and sham PAP after 6 months.[141, 142] However, analyses stratified by OSA severity found that greater improvement in QOL may occur for those with

severe OSA treated with PAP who used it more than 4 hours per night (compared with those treated with sham PAP; between-group difference on SAQLI, 0.2; $p<0.05$).[141, 142] We found no other study that reported the difference between the effect on health outcomes of PAP versus sham PAP for populations defined by age, sex, BMI, or severity of OSA.

MADs

We included 12 RCTs (reported in 15 articles) assessing the effect of MADs on health outcomes, including mortality, QOL, cognitive impairment, CV events, headaches, and ESS (**Appendix E Table 5**).[164, 177, 206-218] Four studies compared MADs with sham devices that did not advance the mandible,[206, 207, 216-218] one compared an MAD with a placebo tablet,[164] two compared MADs with no treatment,[209, 215] and one compared an MAD with conservative management of OSA with weight loss.[177] All studies recruited participants with known or suspected OSA from specialty clinics, such as sleep medicine or otolaryngology. Nine studies were conducted in Europe, two in Australia,[164, 211] and one in Hong Kong.[177] Treatment durations ranged from 4 to 12 weeks for most studies; however, one lasted for only 1 week[209] and one for 24 weeks.[206] The mean age of enrolled participants ranged from 46 to 58 years. The vast majority of participants were men, with women comprising 14 to 32 percent in the 11 trials reporting sex. No study reported the percentage of minority participants. Almost all studies included participants with mild to moderate OSA, and six studies also included participants with severe OSA.[177, 208, 209, 211, 214, 218] One study included participants with only severe OSA.[216]

Mortality

Among the four trials that reported on mortality over 1 to 12 weeks,[164, 209, 215, 218] three reported no participant deaths. The other trial reported one death in the no-treatment group.[218]

QOL

Six included trials reported at least one QOL measure.[164, 177, 206, 207, 215, 217, 218] All six used the SF-36, two of the six also used the SAQLI[177, 215] and three of the six also used the FOSQ.[164, 215, 217] Because of heterogeneity in the reporting of SF-36 outcomes, the results could not be pooled in a meta-analysis. Overall, results were mixed, with some studies finding no significant improvement in QOL from using MADs,[177, 206, 207, 217] some reporting possible benefits for some measures or subscales but not for others,[164, 218] and some reporting benefits for some overall QOL scores.[215] 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 using MADs for improving QOL.

SF-36

The two trials (n=39 and n=91) that compared an MAD with a sham device found no significant difference in multiple SF-36 subscores.[206, 207, 217] A four-arm crossover trial (n=90) of three 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.[215] 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.[177] 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).[218] 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.[164]

Sleep-Related QOL

The trial that compared an MAD with conservative management for 10 weeks found significant improvements in the Emotional and Symptoms subscores but not in the total SAQLI score.[177] The four-arm crossover trial that compared three types of MADs (each for 6 weeks) found significant improvement in the total SAQLI score for all devices and in nearly all subscores for all devices.[215] 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.[164]

ESS

Ten trials included in our meta-analysis reported on change in ESS among groups randomized to MAD or to an inactive control.[164, 177, 208-211, 214-216, 218] Our meta-analyses found that MADs improved ESS scores more than controls (-1.67 [95% CI, -2.09 to -1.25]; 10 trials, 1,540 participants; I^2=36%) (**Appendix F Figure 5**). The pool mean difference, however, falls below the range considered an MCID for the ESS.[204, 205] One trial that did not provide sufficient data to be included in the meta-analysis found consistent results.[217]

Other Health Outcomes

We included one trial assessing each of the following outcomes for participants using MADs over 6 to 12 weeks: cognitive impairment,[164] MVAs,[215] CV events,[215] and headaches.[217] Specific data are provided in **Appendix E Table 6**. Because of unknown consistency, imprecision, and very small numbers of events, findings are insufficient to make conclusions about the potential benefits of MADs for these outcomes.

Subpopulations

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

KQ 6. What Are the Harms Associated With Treatment of OSA Using PAP or MADs, Including for Specific Subgroups of Interest?

Reporting of harms in the included studies was sparse. Most did not report information about harms. Nineteen RCTs (reported in 24 articles) reported on harms associated with treatment of OSA, including 9 trials of PAP,[137, 141, 142, 156, 157, 171, 177, 189, 193, 201, 219, 220] 9 of MADs,[177, 206, 207, 209-

[218] and 1 of PAP and MAD.[177] Characteristics and detailed results of all 19 studies reporting harms are provided in **Appendix E Tables 2**, **3**, **5**, **7**, and **8**.

PAP

Of the 10 included RCTs of PAP, six compared PAP with a sham device,[137, 141, 142, 156, 157, 201, 219, 220] and four compared PAP with another control (e.g., oral placebo, usual care).[171, 177, 189, 193] Most studies enrolled fewer than 100 persons; one study[189] enrolled 111 participants, another study[157] enrolled 281 participants, a third study[193] enrolled 298 participants, and the Apnea Positive Pressure Long-term Efficacy Study[141, 142] enrolled more than 1,000 participants. The majority of enrollees were male, the mean age ranged from 42 to 62 years, and most participants were overweight or obese (mean BMI, 27–39 kg/m^2). Most of the studies followed patients for 8 to 12 weeks, and two lasted 24 weeks.[141, 142, 193] In general, harms related to PAP treatment were likely short-lived and could be alleviated by discontinuing treatment with PAP or by supplementing PAP with additional interventions. Overall, 1 to 47 percent of participants in trials of PAP reporting any harms had specific adverse events while using PAP, including claustrophobia, oral or nasal dryness, eye or skin irritation, rash, nosebleeds, and pain.

Across four studies,[177, 189, 201, 219, 220] 11 percent of patients receiving therapeutic PAP reported irritation compared with 1 percent of patients in the control group. In one study,[141, 142] rash was reported by significantly more patients receiving therapeutic PAP than by participants receiving sham PAP (18% vs. 11%; p=0.001). Claustrophobia was reported in one trial by a single patient (2%) receiving sham PAP, but by none receiving therapeutic PAP.[201, 220] One study reported three nosebleeds—one in the PAP group (2%) and two in the control group (4%)[189]—and another study reported one (0.7%) nosebleed in the PAP group and none in the control group.[193] In two studies, 12 percent of patients reported oral dryness, and 47 percent of patients reported nasal dryness in the therapeutic PAP group compared with 0 percent in the usual care arm.[171, 177] Three trials reported on pain in the PAP group;[171, 193, 201, 220] a fourth trial reported on temporomandibular joint pain,[177] but no patient reported an event. One study contained one report each (2%) of ear pain and noncardiac chest pain in the therapeutic PAP arm; no patient in the control arm reported pain.[201, 220] In the second RCT, no patient in the active PAP arm reported pain compared with one patient (3%) in the control arm who reported chest pain and arm pain.[171] The third study reported two cases of pain: one in the PAP group (0.7%) and one in the control group (0.7%).[193] A single trial reported on both excess salivation and dental issues, such as tooth damage or loosening, but no patient reported either event.[177] No study reported the need for additional sleep medication as a consequence of the intervention.

MADs

Ten RCTs reported harms related to MAD use.[177, 206, 207, 209-218] Most RCTs (k=6) lasted 4 to 8 weeks, one lasted a single week,[209] one lasted 10 weeks,[177] one lasted 12 weeks,[210] and one lasted 24 weeks.[206, 207] Across three studies that reported any discontinuation of treatment because of adverse events, 7 percent of patients in the active MAD group discontinued MAD use due to harms compared with 1 percent of patients in the control group.[177, 215, 218] No study reported rash, claustrophobia, nosebleed, or the need for additional sleep medication.

In four studies, rates of oral dryness ranged from 5 to 33 percent in the active MAD group compared with 0 to 3 percent in the control group.[177, 206, 207, 210, 215] Six studies reported rates of excess salivation.[177, 206, 207, 210-213, 215, 217] Three of these reported rates of excessive salivation from 23 to 68 percent in the active treatment arms compared with 0 to 3 percent in the sham group or no-treatment group.[177, 206, 207, 215] One of the six studies reported a higher rate of excessive salivation in the sham MAD arm than in the active treatment arm (58% and 36%, respectively).[210] Another reported a significantly higher rate of hypersalivation but did not report the number of patients who experienced this outcome.[217] The remaining study reported no significant difference in excess salivation between the MAD and sham groups but also did not report the respective numbers of patients.[211-213]

All 10 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 persistently, 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 the sham group, no-treatment group, or conservative management group. Two studies reported that there was a statistically significant difference only in the percentage who experienced jaw discomfort and tooth tenderness in the MAD group compared with that in the sham group.[211-213, 217] One trial (n=150) measured common harms on one scale by asking participants to rate presence and severity (0, absent; 1, mild; 2, moderate; 3, severe) of the following: jaw pain, tooth pain, muscle stiffness, dry mouth, hypersalivation, and occlusal changes.[216] There was no significant difference between MAD and sham groups on mean scores at 8 weeks (2 vs. 2; p=0.14).

Chapter 4. Discussion

Summary of Evidence

Table 4 provides a summary of findings for this evidence review. This table is organized by KQ, then by questionnaire, prediction tool, test, or intervention and provides a summary of outcomes with a description of their precision, quality, and applicability.

Evidence for Benefits and Harms of Screening for OSA

We did not identify any eligible study directly evaluating the benefits or harms of screening for OSA compared with those of no screening. Potential harms include overdiagnosis and overtreatment for asymptomatic persons with OSA (AHI ≥5) who never would have had symptoms of OSA or adverse health outcomes from OSA. Other potential harms include costs associated with referrals and additional testing (e.g., future PSG for follow-up care). Furthermore, we found no study evaluating the effect of OSA screening on psychological outcomes such as distress due to labeling or stigma.

Appendix A Contextual Question 1 describes potential barriers to undergoing diagnostic testing for OSA, which are important considerations for both screening and detection of persons at risk for OSA during routine care (in the absence of a formal screening program). Studies assessing why persons referred to a sleep lab did not follow up highlight the following reasons: misconceptions about OSA (e.g., lack of understanding of the disease, such as conflating snoring with OSA), work responsibilities, and financial and transportation difficulties. Some evidence suggests that patients with signs and symptoms of OSA such as snoring or gasping and sleepiness are more likely to be adherent to sleep testing than patients without symptoms. Other potential barriers include structural factors, such as geographical distance from specialists and sleep study centers, and factors specific to healthcare providers (e.g., inexperience with OSA leading to under recognition of obvious signs/symptoms that may benefit from diagnostic testing for OSA).

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. No approach was assessed by more than two included studies. Although four studies[115-118] assessed the STOP-BANG, only two of them[115, 118] examined the STOP-BANG without modifications or additional screeners. Findings from these two studies were consistent; both found very good sensitivity but poor specificity. Two studies that modified the STOP-BANG[116, 117] found modest sensitivity and specificity. The other studies assessing the STOP-BANG used different scoring criteria to determine a positive screening test. The only screening approach suggesting possible accuracy evaluated by two studies was the MVAP score followed by unattended HST for detecting severe OSAS (AHI ≥30 and ESS >10). The AUC was approximately 0.8, with a sensitivity around 90 percent and a specificity ranging from 72 to 76 percent.[113, 114] Although

using the MVAP score followed by unattended HST may have promise for screening, the evidence was limited by potential spectrum bias[221-225] due to oversampling of high-risk participants and of those with OSA and OSAS, which may substantially overestimate the accuracy of using this approach to screen for OSA in the general population. Such overestimation was illustrated by a study evaluating the BQ, 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.[112] The included studies evaluating MVAP enrolled populations with a high prevalence of OSAS (≥25%),[113, 114] OSA (AHI ≥5 for 80% of participants, and mean AHI of 22.5),[114] and sleepiness (74%).[113] In addition, no study prospectively measured calibration, which is often assessed by plotting the predicted risk versus the observed event rate,[121] and no study assessed the clinical utility for improving health outcomes. Two included studies evaluating the BQ and STOP-BANG enrolled different populations and found inconsistent results.

We included fewer studies evaluating questionnaires or clinical prediction tools than some previously published reviews and guidelines,[21, 47, 226] primarily because of our requirement to include studies that enrolled asymptomatic adults or adults with unrecognized symptoms of OSA; referral populations (e.g., to sleep clinics) were not eligible. Previous reviews and guidelines focused generally on diagnostic testing (of adults with symptoms suggestive of disordered sleep) rather than on screening (of asymptomatic persons with OSA or those with unrecognized symptoms of OSA). Nevertheless, these reviews and guidelines generally reported low overall quality/strength of evidence for questionnaires and prediction tools.

Benefits and Harms of Treatment for OSA

Our review found consistent evidence from good- and fair-quality RCTs that PAP reduces excessive sleepiness and may improve general health–related QOL and sleep-related QOL. However, benefit associated with PAP for both general health-related QOL and sleep-related QOL measures falls short of the range considered an MCID (**Table 3**), and the clinical significance of the 2-point mean reduction on the ESS is somewhat uncertain. For excessive sleepiness, our data suggest a clinically significant reduction in most included trials because 85 percent of the trials in our meta-analysis for ESS with mean baseline ESS scores of 10 or greater (indicating EDS) reported mean endpoint ESS scores in the normal range of less than 10[227, 228] for the PAP groups (mean endpoint ESS <8). However, the threshold for a clinically significant change in ESS is somewhat uncertain. Although recent SRs noted that experts consider a 1-point change in ESS clinically significant,[47] other sources suggest a 2- to 3-point change[204, 205] or greater change—one of at least 3 or 4 points—should be the clinically significant threshold for its sample size calculations or interpretation of findings.[229-231] Also, the American College of Chest Physicians' outcome experts evaluating the ESS informally stated that a clinically significant change in the ESS probably is at least 3 points and cited a specific example that a reduction of 1 point (e.g., from 3 [high] to 2 [moderate]) on two out of seven ESS domains was unlikely to be clinically relevant.[232] Regardless of the clinically significant threshold level, the subjective nature of the ESS creates potential bias in trials of treatment (e.g., overreporting of improvements in sleepiness after receiving treatment), and some authors have raised concerns about its construct validity (i.e., authors have expressed uncertainty regarding whether it is an accurate measure of sleepiness).[233-235] 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 Sleep Heart Health Study (SHHS)[236] (5,816 participants; mean age, 63 years; 52.5% women) reported that EDS was associated strongly with reduced QOL after adjusting for confounding variables (e.g., age, ethnicity) for both sexes. Sleepiness has also been linked to MVAs in multiple observational studies.[50, 52, 237] 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 had multiple MVAs 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 MVA history (retrospectively).[50] This study was limited by its retrospective design and potential confounding. Considering education and usual alcohol consumption did not alter the OR. However, none of its measures of perceived sleepiness (including those derived from the ESS) was 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 the ESS) had about twice the odds of having experienced a self-reported MVA during the previous 3 years (OR, 1.91 [95% CI, 1.09 to 3.35]) and an even greater odds of having experienced multiple MVAs during the same period (OR, 2.67 [95% CI, 1.29 to 5.52]).[237]

For BP reduction (KQ 4), recent systematic reviews found that MAD and PAP are associated with a reduction in BP of 2 to 3 mm Hg, and one review limited to populations with resistant hypertension found a slightly higher mean reduction (5 mm Hg). Some experts suggest that a difference of more than 9/10 mm Hg (SBP/DBP) is clinically meaningful for patients.[238-240] However, guidelines have suggested that across a population, a smaller reduction in SBP (2 to 3 mm Hg) could result in a clinically significant reduction in CV mortality (reduction of 4% to 5% for CHD and 6% to 8% for stroke).[241] Even though MAD and PAP have been shown to reduce mean BP, no trials to date have shown a significant reduction in mortality or CVD.

We found that MADs also reduce excessive sleepiness, although the magnitude of effects was generally less than that with PAP, and BP reduction was not established based on a recent review.[123] Although we did not evaluate head-to-head studies (e.g., those directly comparing MADs with PAP), previous comparative effectiveness reviews examining head-to-head trials reported smaller effect sizes for reducing AHI with MADs than with PAP.[47]

Evidence on most health outcomes was limited (i.e., too few RCTs reported on outcomes or too few events occurred to evaluate the effectiveness of PAP for reducing mortality, CV events, or MVAs). As summarized in **Appendix A Contextual Question 2**, there is a relatively large body of observational evidence supporting an association between severe OSA (AHI ≥30) and increased risk of many adverse health outcomes, including CV events, mortality, and cognitive impairment. Some studies suggest that the risk of such outcomes increases with each level of OSA severity, which may indicate a dose-response effect; however, this finding is not consistent across all studies or outcomes. Lastly, findings of increased risk associated with severe OSA are the strongest among male populations; however, it is difficult to assess if these relationships do not hold for female populations or if they are due to more sparse evidence on female populations. Observational studies focused on this association are limited, however, primarily due to potential confounding.

Reporting of harms from treatment in the included studies was sparse. Most did not report information about harms. In general, the adverse events related to PAP treatment were likely short-lived and could be alleviated by discontinuing treatment with PAP or by supplementing PAP with additional interventions. Common adverse events included oral or nasal dryness, eye or skin irritation, and rash. Common adverse effects from MADs included oral or nasal dryness, excessive salivation, and jaw discomfort. No included study reported on psychosocial harms of treatment, such as disruption of partner sleeping (e.g., because of the noise of PAP). Such adverse effects may limit patient adherence to treatment. However, a recent review of the effect of treatment for OSA reported several studies in which partners of patients treated with PAP indicated better quality of sleep and reduced sleep disturbance.[242] A wide range (from 30% to 85%) of adherence to usage recommendations for PAP has been reported.[243] An SR 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 treatment with PAP over 4 years and patients use PAP for an average of 5 hours per night; data on adherence to treatment with MADs were too limited to provide adherence rates.[47] This review also found that the AHI and the ESS are independent predictors of PAP adherence.[47] A recent Cochrane SR of 33 studies (2,047 participants) found low- to moderate-quality evidence that three types of interventions can increase PAP usage in PAP-naive participants with moderate to severe OSAS.[243] These included supportive interventions that encourage persons to continue to use PAP 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 PAP usage on daytime sleepiness, QOL, and long-term CV risks remains unclear.

Limitations

No studies were identified comparing screened and unscreened populations, which limits our ability to make conclusions about the direct benefit or harms of screening for OSA in primary care settings. 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 6). For the first question in that indirect pathway (KQ 2), we found limited evidence that one screening approach (MVAP followed by unattended HST) might be useful to screen for severe OSAS, but the evidence was limited by potential spectrum bias, and no study prospectively assessed calibration or clinical utility for improving health outcomes. Studies of other screening questionnaires were heterogeneous in terms of enrolled populations and found inconsistent results.

We required studies to use in-laboratory PSG as the reference standard for KQ 2. This is similar to the approach used in previous SRs. For KQ 2, this resulted in exclusion of a large study from the SHHS that included 4,770 community participants and that reported on the STOP, STOP-BANG, and ESS questionnaires. This study reported a sensitivity from 39 (ESS ≥11) to 87 percent (STOP-BANG) and specificity from 43 (STOP-BANG) to 71 percent (ESS) for predicting moderate to severe OSA (RDI ≥15).[244] NLR ranged from 0.3 to 0.85, indicating minimal to small decreases in the likelihood of disease, and PLR 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 SRs have found limited utility of individual findings. A previous review of clinical examination accuracy, which was not limited to asymptomatic patients with OSA or those with unrecognized symptoms of OSA, 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 an AHI of 10 or greater.[21] This review found that many symptoms and signs provide limited information in determining the likelihood of OSA.[21]

We did not evaluate every possible outcome or intervention for OSA. We chose the outcomes that are most commonly reported and most potentially clinically meaningful. Our review was limited to interventions considered first-line treatments for persons with newly detected OSA (PAP and MAD). We did not include interventions that are primarily offered to persons who do not benefit from or tolerate PAP or MAD. We did not evaluate some treatments that may have potential benefits, such as oropharyngeal exercises,[245, 246] playing the didgeridoo, or using nasal steroids for treating allergic rhinitis (or similar treatments that might secondarily improve OSA by treating another condition).[247-249] Nevertheless, previous reviews and clinical practice guidelines suggest that the potential benefits of such treatments are limited or uncertain.[47, 96] We limited eligible study designs to RCTs for evaluating treatment benefits, which possibly 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.

Some of our meta-analyses of RCTs evaluating the benefits of PAP (KQ 5) found substantial statistical heterogeneity. We did not find a clear explanation for the statistical heterogeneity, but possible explanations include variation in PAP devices (e.g., machines, masks, humidifiers, filters, cushions), participant characteristics (e.g., studies with a 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 cut points for oxygen desaturation are used to define hypopnea; some studies define hypopnea as requiring either oxygen desaturation or an EEG arousal, and some studies do not clearly define hypopnea. A publication from the SHHS demonstrated the potential impact of variation in hypopnea definitions on the prevalence of OSA, reporting that varying the definition in an otherwise healthy older population increased the prevalence from roughly 50 percent (using the Centers for Medicare & Medicaid Services' definition of 4% oxygen desaturation) to greater than 80 percent (using the AASM's 2012 definition of either 3% oxygen desaturation or an EEG arousal).[250, 251] 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, the vast majority of trials that included participants with EDS at baseline (ESS ≥10) reported mean endpoint ESS scores well into the normal range (<8) for the PAP-treated groups.

Future Research Needs

To better understand the potential effectiveness of screening for OSA, RCTs of asymptomatic persons with OSA (or those with unrecognized symptoms of OSA) that directly compare screening with no screening and assess health outcomes (i.e., trials that address KQ 1, the overarching question) are needed. To better determine the accuracy of screening questionnaires and clinical prediction tools when used in the general population (related to 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 unattended HST) as well as other approaches assessed in similar populations for which we found few studies, such as the BQ and STOP-BANG Questionnaire. Trials of treatment (PAP and MAD) that enroll participants who are screen-detected from primary care settings are needed; results of trials that enrolled participants referred for OSA symptoms and other sleep complaints may not be applicable to populations who would be screen-detected. In addition, trials of common treatments that evaluate whether treatments improve other health outcomes (except for sleep-related QOL), such as CV events, are needed.

Conclusion

The clinical utility of potential screening tools is uncertain. Although screening with MVAP followed by unattended HST may accurately distinguish persons in the general population who are more or less likely to have OSA, current data are limited by potential spectrum bias, with an oversampling of high-risk participants and those with OSA and OSAS. Further, we found no study that prospectively evaluated screening questionnaires or clinical prediction tools to report the calibration or the clinical utility for improving health outcomes. Other eligible screening questionnaires (BQ and STOP-BANG) were evaluated by two studies each and found inconsistent results. Treatment with PAP and MADs improve intermediate outcomes—PAP effectively reduces AHI to a normal or near-normal level and reduces BP; MADs also reduce AHI and BP, although the magnitudes of effects were generally less than those with PAP. Although consistent observational evidence has established that persons with severe or moderate to severe OSA die at twice the rate of that of controls, trials of PAP and other treatments have not satisfactorily evaluated whether treatment reduces mortality or improves most other health outcomes, barring evidence of possible benefit for reduction in EDS and improved sleep-related QOL.

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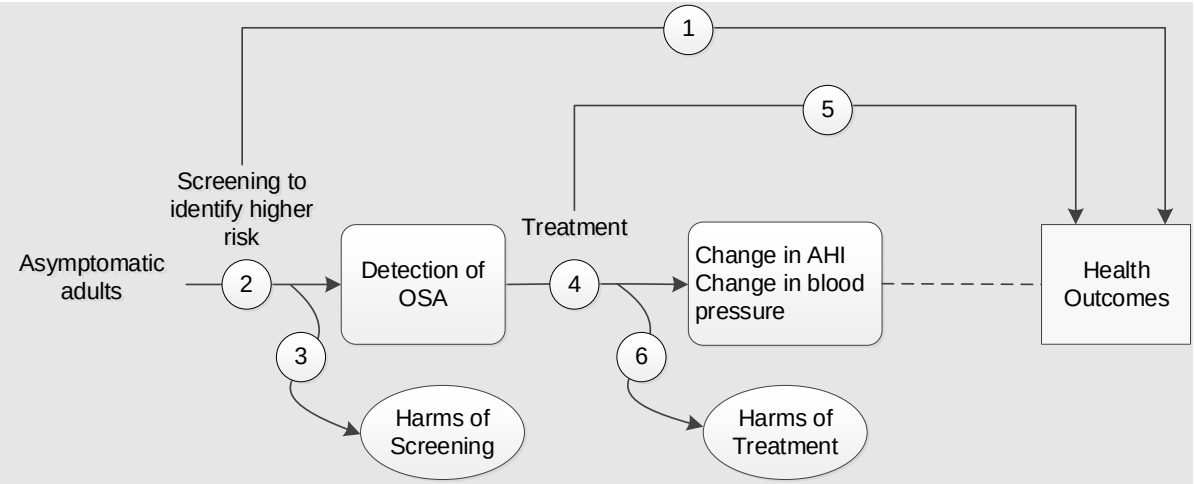
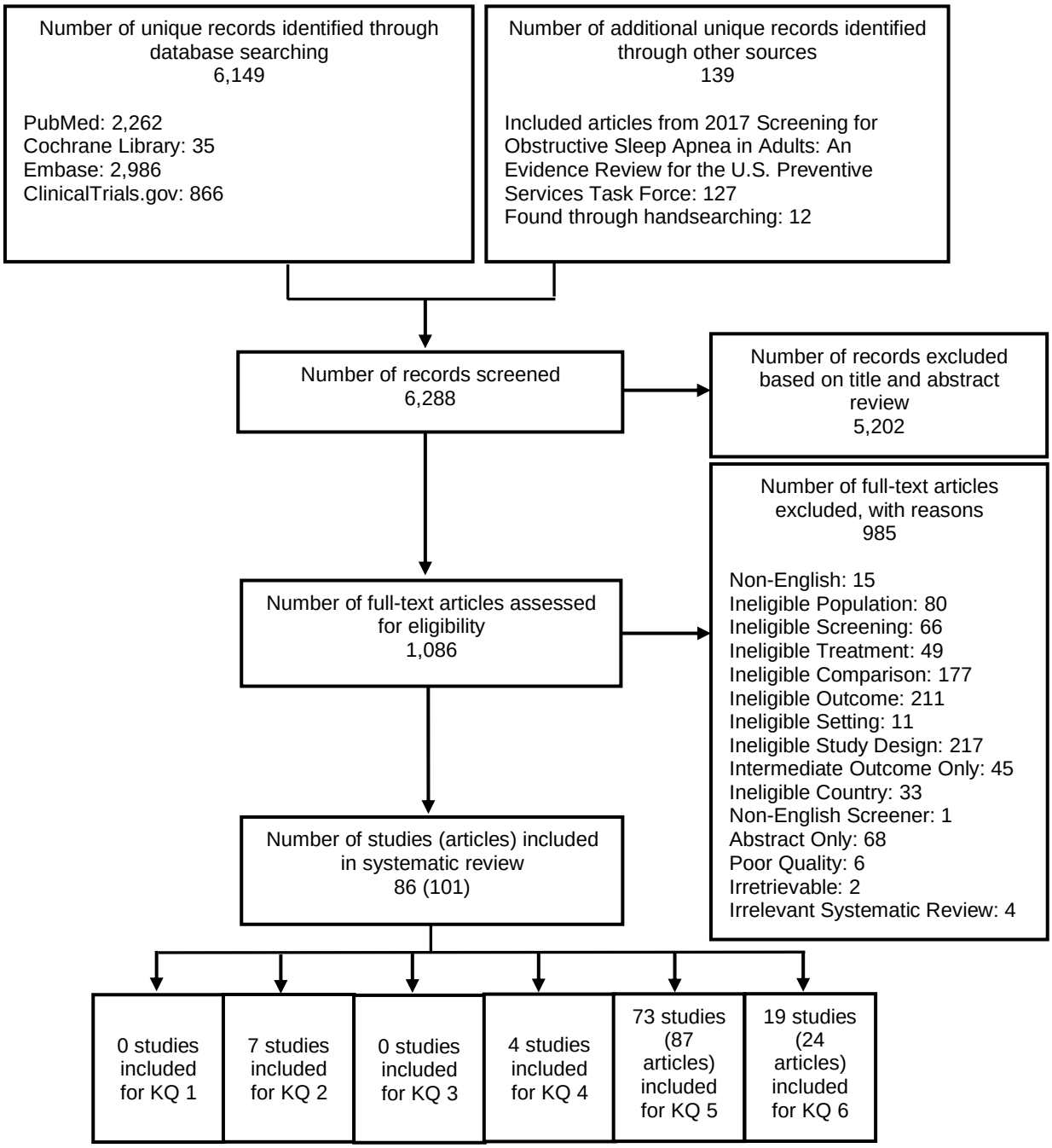
Figure 1. Analytic Framework



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

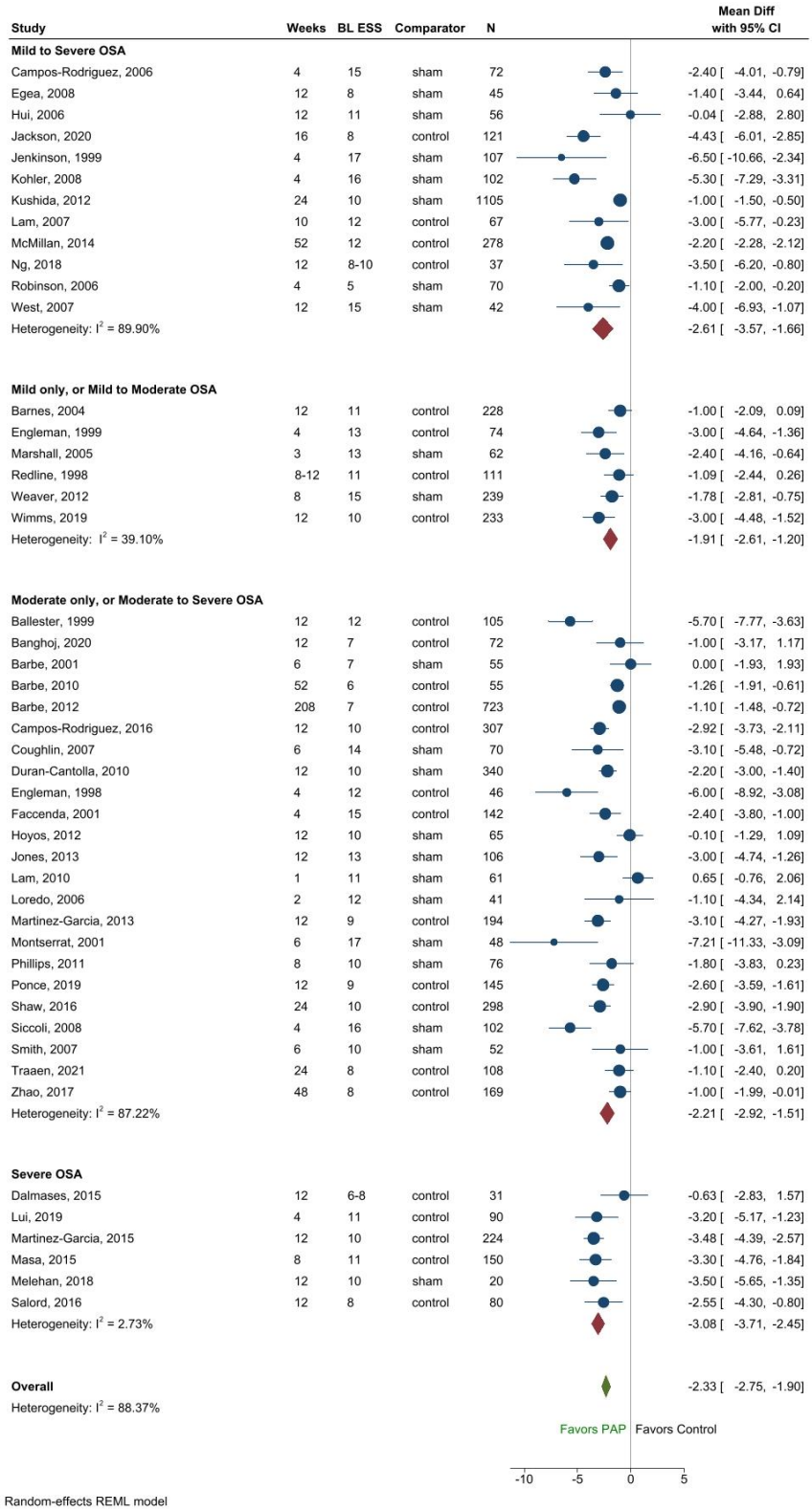
Figure 2. Summary of Evidence Search and Selection



Note: The sum of the number of studies per KQ exceeds the total number of studies because some studies were applicable to multiple KQs.

Abbreviation: KQ=key question.

Figure 3. Comparison of PAP vs. Inactive Control for Change in ESS



Abbreviations: BL=baseline; CI=confidence interval; Diff=difference; ESS=Epworth Sleepiness Score; N=sample size; PAP=positive airway pressure; REML=restricted maximum likelihood; vs.=versus.

Table 1. Characteristics of Included Studies Assessing the Accuracy of Clinical Prediction Tools or Screening Questionnaires (KQ 2)

First Author, Year Country	N	Study Design	Study Quality	Participants	Name of Questionnaire(s)/ Tool(s)	Mean Age (SD)	% F	% Race/ Ethnicity	Mean BMI (SD)	Mean AHI (SD)	% With HTN	% With OSA
Hrubos-Strom, 2011[112] Norway	518*	Cross-sectional	Fair	Randomly drawn from Norwegian National Population Register	BQ (Norwegian translation)	48 (11.2)	45	NR	28 (4.8)	Median 6.4 (NR†)	27	NR
Morales, 2012[113] United States	452	Cross-sectional	Fair	Medicare recipients from greater Philadelphia metro region, most with some daytime sleepiness‡	MVAP score; MVAP score + AHI from unattended HST	71 (5.4)	70	African American: 61 Caucasian: 36	30 (6.2)	NR	NR	Any OSA: NR Any OSAS (AHI ≥5 and ESS >10): 27§
Gurubhagav-atula, 2013[114] United States	250	Cross-sectional	Fair	U.S. adults with HTN‖ from internal medicine practices and an HTN clinic	MVAP score; MVAP score + AHI from unattended HST	53 (7.7)	20	African American: 59 Caucasian: 40	32 (7.4)	22.5 (22.9)	100	Of the 79% who had in-lab PSG: Any OSA: 80¶ OSAS: 25#
Edmonds, 2019[115] United States	43	Cross-sectional	Fair	U.S. adults with DM2 from a general internal medicine clinic	STOP-BANG, BQ	NR	53	NR	38 (7.7)	31.2 (28.1)	NR	Mild (AHI 5–14): 28 Mod (AHI 15–29): 26 Severe (AHI ≥30): 37
Jorge, 2019[116] Spain	91	Cross-sectional	Fair	Spanish adults with a recent diagnosis of mild to mod AD	Modified STOP-BANG**	Median (IQR) 76 (73–80)	64	NR	Median (IQR) 28 (25.2 to 30.2)	20.7 (10.6 to 40.3)	57	Mild (AHI: 5–14): 26.4 Mod (AHI 15–30): 25.3 Severe (AHI >30): 37.4
Shin, 2021[117]	1,033††	Cross-sectional	Fair	Korean adults enrolled in a population-based cohort study	Modified STOP-BANG‡‡	59 (7.9)	48	Asian: 100	25 (3.0)	7.3 (8, 9)	38	Mild (AHI 5–14): 32.4 Mod (AHI 15–29): 10.1 Severe (AHI ≥30): 3.1
Selvanathan, 2021[118,§§]	202/ 199‖	Cross-sectional	Fair	Adults on opioids for chronic pain	STOP-BANG STOP-BANG + resting daytime SpO_2	53 (12.8)	58	NR	29 (6.4)	Median (IQR) 6.5 (2.3 to 19.4)	33	NR

* The data in this row describe the 518 participants who underwent PSG. The 518 were a subset of the larger study population of 16,302 who completed the BQ. The mean age of the larger study population was 48 years, 53% were female, the mean BMI (SD) was 26 (4.3), and 14% had HTN.

† SD was not reported, but 25th and 75th percentiles were 1.7 and 18.3, respectively.

‡ 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.

§ Mild (AHI 5–15 and ESS >10): 9%; at least mod (AHI ≥15 and ESS >10): 17%; mod (AHI 15–30 and ESS >10): 8%; severe (AHI ≥30 and ESS >10): 8%.

‖ Required to have BP ≥140/90 or to be on antihypertensive medications.

¶ Mild: 34%; mod: 22%; severe: 25%.

At least mild (AHI ≥5 and ESS >10): 25%; severe (AHI ≥30 and ESS >10): 7.6%.

** Modified STOP-BANG (age older than 70 years, BMI >26 kg/m^2; neck circumference >26.5 cm).

†† Validation sample only.

Table 1. Characteristics of Included Studies Assessing the Accuracy of Clinical Prediction Tools or Screening Questionnaires (KQ 2)

[ǂǂ] Modified STOP-BANG (age 5–64 years 1 point, age ≥65 years 2 points; and waist circumference >85, snoring; observed apnea; high blood pressure; BMI >25 kg/m^2, each 1 point).
[§§] Although this is a 2-stage study, we only report the findings from the first stage in which all patients are included.
[ǁ] The n of 202 represents those who received the STOP-BANG and PSG; the n of 199 includes those who received the STOP-BANG, PSG, and resting daytime (SpO_2).

Abbreviations: AD=Alzheimer's disease; AHI=apnea-hypopnea index; BMI=body mass index; BP=blood pressure; BQ=Berlin Questionnaire; DM2=type 2 diabetes; ESS=Epworth Sleepiness Scale; F=female; HST=home sleep testing; HTN=hypertension; IQR=interquartile range; KQ=key question; mod=moderate; MVAP=Multivariable Apnea Prediction; N=sample size; NR=not reported; OSA=obstructive sleep apnea; OSAS=obstructive sleep apnea syndrome; PSG=polysomnography; SD=standard deviation; STOP-BANG=Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference, Gender; U.S.=United States.

Table 2. Results of Included Studies Assessing the Accuracy of Clinical Prediction Tools or Screening Questionnaires (KQ 2)

First Author, Year	Cutoff Value of Screening Questionnaire(s)/ Tool(s)	Reference Standard Definition of OSA Diagnosis	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Calibration	Other Accuracy Measures (95% CI)
Hrubos-Strom, 2011[112]	BQ ≥2 positive categories	AHI ≥5*	37.2 (36.0 to 38.4)	84.0 (83.2 to 84.7)	NR	NR	PPV=61.3 (59.7 to 62.9) NPV=66.2 (65.3 to 67.1) PLR=2.3 (2.2 to 2.5) NLR=0.8 (0.7 to 0.8)
Hrubos-Strom, 2011[112]	BQ ≥2 positive categories	AHI ≥15*	43.0 (41.2 to 44.8)	79.7 (79.0 to 80.5)	NR	NR	PPV=33.5 (32.0 to 35.0) NPV=85.5 (84.8 to 86.1) PLR=2.1 (2.0 to 2.3) NLR=0.7 (0.7 to 0.7)
Morales, 2012[113]	MVAP=0.49	Severe OSAS (AHI ≥30 and ESS >10)	90.0 (NR)	64.4 (NR)	0.78 (0.71 to 0.85)	NR	NLR=0.141 (NR) NPTP=1.1% (NR)
Morales, 2012[113]	MVAP+HST†=uAHI 15	Severe OSAS (AHI ≥30 and ESS >10)	90.9 (NR)	75.7 (NR)	0.83 (0.77 to 0.90)	NR	NLR=0.120 (NR) NPTP=1.0% (NR)
Gurubhagavatula, 2013[114]	MVAP=0.483	Severe OSAS (AHI ≥30 and ESS >10)	91.5 (NR)	43.9 (NR)	0.68 (0.67 to 0.70)	NR	NLR=0.190 (NR) NPTP=0.015 (NR)
Gurubhagavatula, 2013[114]	MVAP=0.559	Any OSAS (AHI ≥5 and ESS >10)	69.4 (NR)	56.5 (NR)	0.61 (NR)	NR	NLR=0.524 (NR) NPTP=0.148 (NR)
Gurubhagavatula, 2013[114]	MVAP+HST†=uAHI 18	Severe OSAS (AHI ≥30 and ESS >10)	88.2 (NR)	71.6 (NR)	0.80 (0.78 to 0.82)	NR	NLR=0.162 (NR) NPTP=0.015 (NR)
Gurubhagavatula, 2013[114]	MVAP+HST†=uAHI 13.5	Any OSAS (AHI ≥5 and ESS >10)	80.5 (NR)	54.0 (NR)	0.67 (NR)	NR	NLR=0.349 (NR) NPTP=0.104 (NR)
Edmonds, 2019[115]	STOP-BANG ≥3	Mild (AHI 5–14)	87.2 (NR)	0	NR	NR	PPV=89.5 (NR) NPV=0 (NR)
Edmonds, 2019[115]	STOP-BANG ≥3	Mod (AHI 15–29)	92.6 (NR)	18.8 (NR)	NR	NR	PPV=65.8 (NR) NPV=60 (NR)
Edmonds, 2019[115]	STOP-BANG ≥3	Severe (AHI ≥30)	93.8 (NR)	14.8 (NR)	NR	NR	PPV=39.5 (NR) NPV=80 (NR)
Edmonds, 2019[115]	BQ ≥2 positive categories	Mild (AHI 5–14)	79.5 (NR)	0 (NR)	NR	NR	PPV=88.6 (NR) NPV=0 (NR)
Edmonds, 2019[115]	BQ ≥2 positive categories	Mod (AHI 15–29)	88.9 (NR)	31.3 (NR)	NR	NR	PPV=68.6 (NR) NPV=62.5 (NR)
Edmonds, 2019[115]	BQ ≥2 positive categories	Severe (AHI ≥30)	93.8 (NR)	25.9 (NR)	NR	NR	PPV=42.9 (NR) NPV=87.5 (NR)

Table 2. Results of Included Studies Assessing the Accuracy of Clinical Prediction Tools or Screening Questionnaires (KQ 2)

First Author, Year	Cutoff Value of Screening Questionnaire(s)/ Tool(s)	Reference Standard Definition of OSA Diagnosis	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Calibration	Other Accuracy Measures (95% CI)
Jorge, 2019[116]	Modified STOP-BANG (age older than 70 years; BMI >26 kg/m^2; neck circumference >26.5 cm) ≥2 positive categories	Severe (AHI >30)	61 (47 to 74)	76 (59 to 89)	0.72 (0.61 to 0.83)	NR	PPV=81 (66 to 91) NPV=54 (39 to 69)
Shin, 2021[117]	Modified STOP-BANG ≥3 (snoring; observed apnea; high blood pressure; BMI >25 kg/m^2; age 5–64 years 1 point, ≥65 years 2 points; waist circumference >85 cm; diabetes; male)	All (AHI ≥5)	62.3 (60.5 to 64.2)	64.5 (62.9 to 66)	0.73 (0.70 to 0.76)	NR	PPV=64 (63.4 to 64.4) NPV=71.8 (71.1 to 72.5)
Shin, 2021[117]	Modified STOP-BANG ≥3 (snoring; observed apnea; high blood pressure; BMI >25 kg/m; age 5–64 years 1 point, ≥65 years 2 points; waist circumference >85 cm; diabetes; male)	Mild to moderate (5 < AHI <30)	62.0 (60.1 to 63.9)	63.8 (62.2 to 65.4)	0.72 (0.69 to 0.75)	NR	PPV=61.6 (61.0 to 62.3) NPV=72.6 (71.9 to 73.3)
Shin, 2021[117]	Modified STOP-BANG ≥3 (snoring; observed apnea; high blood pressure; BMI >25 kg/m^2; age 5–64 years 1 point, ≥65 years 2 points; waist circumference >85 cm; diabetes; male)	Severe (AHI ≥30)	79.1 (77.3 to 80.9)	53.3 (51.6 to 54.9)	0.78 (0.72 to 0.84)	NR	PPV=6.03 (6.89 to 6.17) NPV=99.2 (99.1 to 99.2)
Selvanathan, 2021[118]	STOP-BANG ≥3‡	Moderate to Severe (AHI ≥15)	89.2 (80.1 to 95.0)	38.0 (33.6 to 40.7)	NR	NR	NR
Selvanathan, 2021[118]	STOP-BANG ≥3 or resting daytime SpO_2 ≤95%‡	All (AHI ≥5)	92.9 (87.8 to 96.0)	31.6 (24.5 to 37.0)	NR	NR	PPV=67.3 (63.9 to 69.8) NPV=73.5 (57.0 to 86.0) PLR=1.4 (1.2 to 1.5) NLR=0.2 (0.1 to 0.5)
Selvanathan, 2021[118]	STOP-BANG ≥3 or resting daytime SpO_2 ≤95%‡	Moderate to severe (AHI ≥15)	95.4 (87.7 to 98.8)	23.1 (19.4 to 24.8)	NR	NR	PPV=37.6 (34.6 to 38.9) NPV=91.2 (76.5 to 97.7) PLR=1.24 (1.0 to 1.3) NLR=0.2 (0.05 to 0.6)

Table 2. Results of Included Studies Assessing the Accuracy of Clinical Prediction Tools or Screening Questionnaires (KQ 2)

First Author, Year	Cutoff Value of Screening Questionnaire(s)/ Tool(s)	Reference Standard Definition of OSA Diagnosis	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	Calibration	Other Accuracy Measures (95% CI)
Selvanathan, 2021[118]	STOP-BANG ≥3 or resting daytime SpO_2 ≤95%‡	Severe (AHI ≥30)	100 (89.4 to 100)	21.0 (18.6 to 21.0)	NR	NR	PPV=22.4 (20.0 to 22.4) NPV=100 (88.4 to 100) PLR=1.3 (1.1 to 1.3) NLR=infinity

* Estimates were based on a simulated model that adjusted for oversampling of BQ high-risk participants (not just based on findings for the 518 in the clinical sample).

† 2-stage process using MVAP for everyone, and then unattended HST to estimate AHI for those with an intermediate MVAP score.

‡ Although this is a two-stage study, we only report the findings from the first stage in which all patients were included.

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; HST=home sleep testing; KQ=key question; mod=moderate; MVAP=Multivariable Apnea Prediction; NLR=negative likelihood ratio; NPTP=negative post-test probability; NPV=negative predictive value; NR=not reported; OSA=obstructive sleep apnea; OSAS=obstructive sleep apnea syndrome; PLR=positive likelihood ratio; PPV=positive predictive value; STOP-BANG=Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference, Gender; uAHI=unattended AHI from home sleep test; vs.=versus.

Table 3. Summary of Pooled Findings From PAP Treatment Studies

Outcome Measure	Number of Trials	Number of Participants	Effect Size (95% CI)	I^2	Estimated MCID
ESS	47	7,024	MD: -2.33 (-2.75 to -1.90)	88	-2 to -3[204, 205]
SF-36 PCS	13	2,031	MD: 1.53 (0.29 to 2.77)	59	4 to 7[202, 203]
SF-36 MCS	15	2,345	MD: 2.20 (0.95 to 3.44)	64	4 to 7
Sleep-related QOL: all measures	17	3,083	SMD: 0.30 (0.19 to 0.42)	55	NA*
Sleep-related QOL: FOSQ only	10	1,425	MD: 0.55 (0.05 to 1.06)	70	1.8 to 2.2[252]
Sleep-related QOL: SAQLI only	6	1,725	MD: 0.40 (0.17 to 0.62)	81	1 to 2[253]

* A SMD between 0.2 and 0.4 is considered a small effect size.

Abbreviations: ESS: Epworth Sleepiness Scale; MCID: minimal clinically important difference; MCS=mental component summary score; mod=moderate; MD: mean difference; MVA=motor vehicle accident; PAP=positive airway pressure; PCS=physical component summary score; QOL=quality of life; SAQLI=Sleep Apnea Quality of Life Index; SF-36=Medical Outcome Short-Form (36-Item) Health Survey; SMD=standardized mean difference.

Table 4. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

Key Question (KQ)	Questionnaire, Prediction Tool, Test, or Intervention	Number of Studies and Study Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Study Quality	Body of Evidence Limitations	Overall Strength of Evidence	Applicability
KQ 1. Benefits of screening	NA	No eligible study identified	NA	NA	NA	NA	NA	Insufficient	NA
KQ 2. Accuracy of screening question-naires, clinical prediction tools, and multistep screening approaches	BQ	2 cross-sectional (563)	Varies by OSA threshold (AHI cut point) Sn range: 37% to 94% Sp range: 0% to 84%	Unknown: studies used different reference test thresholds Unknown: one reporting CIs (precise) and one not reporting CIs	Undetected	Fair	Studies enrolled different populations; one with risk of bias due to attrition bias and spectrum bias, and one (enrolling U.S. adults with DM2) with small sample size and risk of bias due to unclear methods for calculating accuracy of OSA categories	Insufficient	Unclear, one study enrolling general population of Norway and one enrolling U.S. adults with DM2
	STOP-BANG Questionnaire	2 cross-sectional (245)	Varies by OSA threshold (AHI cut point) Sn range: 87% to 94% Sp range: 0% to 38%	Unknown: studies used different reference test thresholds Unknown: one reporting CIs (precise) and one not reporting CIs	Undetected	Fair	Studies enrolled different populations, one with DM2 and one who used opioids for chronic pain. Both studies had a moderate risk of bias due to lack of clarity related to screening and reference standard interpreted separately; unclear methods for calculating accuracy of OSA categories	Insufficient	Persons with DM2 and using opioids for chronic pain

Table 4. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

Key Question (KQ)	Questionnaire, Prediction Tool, Test, or Intervention	Number of Studies and Study Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Study Quality	Body of Evidence Limitations	Overall Strength of Evidence	Applicability
KQ 2. Accuracy of screening question-naires, clinical prediction tools, and multistep screening approaches (continued)	Modified STOP-BANG*	1 cross-sectional (91)	Sn and Sp (95% CI) AHI >30: 61 (47 to 74; 76 (59 to 89)	Unknown, single study Imprecise	Undetected	Fair	Single study with risk of bias due to patient selection	Insufficient	Persons with AD
	Modified STOP-BANG†	1 cross-sectional (199)	Sn and Sp (95% CI) AHI ≥5: 93 (88 to 96); 32 (24 to 37) AHI ≥15: 95 (88 to 99); 23 (19 to 25) AHI >30: 100 (89 to 100; 21 (19 to 21)	Unknown, single study Precise	Undetected	Fair	Risk of bias due to unclear methods for calculating accuracy by OSA severity category	Insufficient	Persons using opioids for chronic pain
	MVAP score (for severe OSAS)	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 (1 with inadequate discrimination; 1 with reasonable discrimination) Imprecise	Undetected	Fair	Concern for spectrum bias in both studies; risk of attrition bias in 1	Insufficient	Populations with high prevalence of OSAS (≥25%); only 1 study reported % with *any* OSA (80%); studies included Medicare recipients and adults with HTN
	MVAP score (for any OSAS)	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	Insufficient	Populations with high prevalence of OSAS; studies included Medicare recipients and adults with HTN

Table 4. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

Key Question (KQ)	Questionnaire, Prediction Tool, Test, or Intervention	Number of Studies and Study Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Study Quality	Body of Evidence Limitations	Overall Strength of Evidence	Applicability
KQ 2. Accuracy of screening question-naires, clinical prediction tools, and multistep screening approaches (continued)	MVAP score followed by unattended HST (for severe OSAS)	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 in both studies; risk of attrition bias in one	Low	Populations with high prevalence of OSAS; studies included Medicare recipients and adults with HTN
	MVAP score followed by unattended HST (for any OSAS)	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	Insufficient	Populations with high prevalence of OSAS; studies included Medicare recipients and adults with HTN
KQ 3. Harms associated with screening or subsequent diagnostic testing	NA	No eligible study identified	NA	NA	NA	NA	NA	Insufficient	NA

Table 4. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

Key Question (KQ)	Questionnaire, Prediction Tool, Test, or Intervention	Number of Studies and Study Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Study Quality	Body of Evidence Limitations	Overall Strength of Evidence	Applicability
KQ 4. Efficacy of treatment for improving intermediate outcomes	PAP	AHI: 2 SRs: 1 focused on any OSA severity (11 RCTs, 832) participants) and 1 limited to nonsleepy populations (3 RCTs,1,541 participants) BP: 3 SRs: 1 focused on any OSA severity (12 RCTs,1,919 participants), 1 limited to nonsleepy populations (5 RCTs,1,541 participants), and 1 limited to populations with resistant HTN (23 RCTs; 4,905 participants)	AHI, pooled mean difference: Any OSA severity: -23.41 (-28.51 to -18.30); I^2=93% Nonsleepy populations:-15.57 (-29.32 to -1.82); I^2=87.2% Daytime BP, pooled mean difference: Any severity, SBP: -2.76 (-4.31 to -1.20); I^2=5%; DBP: -1.98 (-3.02 to -0.93); I^2=4%‡ Nonsleepy populations, SBP: -0.51 (-3.39 to 2.38); I^2=84%; DBP: -0.92 (-1.39 to -0.46); I^2=0.0% Populations with resistant HTN: Mean 24-hour SBP: -5.06 (-7.98 to -2.13) Mean 24-hour DBP: -4.21 (-6.50 to -1.93)	Consistent for AHI and BP Precise for AHI and BP; imprecise for BP in pooled estimate limited to nonsleepy populations	Undetected	Good‡	Most trials were ≤12 weeks; estimates associated with significant heterogeneity	Mod for AHI; Mod for BP in overall (any) OSA populations and populations with resistant HTN, low for BP in nonsleepy populations	Referral population with known OSA
	MAD	BP: 1 SR: 11 RCTs (469)	BP: No statistically significant reduction in daytime, nighttime, or 24-hour BP measures	Consistent; Imprecise	Undetected	Good‖	Variations in BP treatment at baseline and limited followup (1–3 months)	Low	Referral population with known OSA

Table 4. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

Key Question (KQ)	Questionnaire, Prediction Tool, Test, or Intervention	Number of Studies and Study Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Study Quality	Body of Evidence Limitations	Overall Strength of Evidence	Applicability
KQ 5. Efficacy of treatment for improving health outcomes	PAP¶	Mortality: 31 RCTs (2,673) ESS: 47 RCTs (7,024) SF-36 PCS: 13 RCTs (2,031) SF-36 MCS: 15 RCTs (2,345) Sleep-related QOL (SAQLI, FOSQ, or QSQ): 17 RCTs (3,083) CV events: 8 RCTs (1,529)	Mortality: No event (27 RCTs) or 1 event (2 RCTs) at ≤12 weeks; no significant difference at 24 weeks (1 RCT: 2 vs. 2), median of 4 years (1 RCT: 8 vs. 3), or median of 5 years ESS: -2.33 (95% CI, -2.75 to -1.90) SF-36 PCS: PAP vs. any comparator: mean difference, 1.53 (95% CI, 0.29 to 2.77) SF-36 MCS: PAP vs. any comparator: mean difference, 2.20 (95% CI, 0.95 to 3.44) SAQLI or FOSQ: PAP vs. any comparator: SMD, 0.30 (95% CI, 0.19 to 0.42) CV events: Overall, too few events were observed to draw conclusions	Mortality and CV events: Consistent for studies of relatively short duration (≤12–24 weeks), unknown for longer duration; Imprecise ESS: Consistent, precise SF-36 PCS, MCS: Mostly consistent, Imprecise Sleep-related QOL: Consistent, precise	Detected for SF-36 outcomes (6 RCTs reported individual SF-36 domains only) Undetected for all other outcomes	7 Good 54 Fair	Study duration may be insufficient to determine benefit for many health outcomes; small number of total events observed across studies for some outcomes (e.g., mortality, CV events)	Moderate for sleep-related QOL and ESS, low for general health-related QOL; insufficient for other health outcomes	Referral population with known OSA

Table 4. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

Key Question (KQ)	Questionnaire, Prediction Tool, Test, or Intervention	Number of Studies and Study Design (Total Sample Size) by Test or Outcome	Summary of Findings by Test or Outcome	Consistency Precision	Reporting Bias	Study Quality	Body of Evidence Limitations	Overall Strength of Evidence	Applicability
KQ 5. Efficacy of treatment for improving health outcomes (continued)	MAD¶	Mortality: 4 RCTs (245) ESS: 10 RCTs (1,540) SF-36 total: 1 RCT (97) SF-36 PCS: 2 RCTs (183) SF-36 MCS: 2 RCTs (183) Sleep-related QOL: 3 RCTs (256)	ESS: Pooled mean difference, -1.67 (95% CI, -2.09 to -1.25) 1 death in no-treatment group in one 4-week RCT (n=93); mixed results for QOL measures	ESS: Consistent Precise Other outcomes: Inconsistent or unknown consistency; Imprecise	Undetected for most; suspected for QOL measures	2 Good 10 Fair	Short study durations (1–12 weeks), small number of studies reporting the outcomes and too few events (for mortality and MVAs)	Moderate for ESS; insufficient for other outcomes	Referral population with known OSA
KQ 6. Harms associated with treatment	PAP	10 RCTs (2,064)	Overall, 1% to 47% had specific adverse events while using PAP. Commonly reported harms were oral or nasal dryness, eye or skin irritation, and rash	Consistent Imprecise	Undetected, but sparse reporting of harms	Fair	High heterogeneity in reporting and findings	Low	Referral population with known OSA
	MAD	10 RCTs (684)	Overall, 17% to 74% had any harms while using MADs. Commonly reported harms were oral or nasal dryness, excess salivation, oral mucosal/dental/jaw symptoms	Inconsistent Imprecise	Undetected, but sparse reporting of harms	Fair	High amount of heterogeneity in reporting and findings; most trials reported harms over a relatively short duration	Low	Referral population with known OSA

* Modified STOP-BANG (age older than 70 years; BMI ≥26 kg/m^2; neck circumference >26.5 cm).

† Modified STOP-BANG (age 5–64 years 1 point, >65 years 2 points; and waist circumference >85, snoring; observed apnea; high blood pressure; BMI >25 kg/m^2 each 1 point).

Table 4. Summary of Evidence for Screening and Treatment of Obstructive Sleep Apnea

[ǂ] Pooled estimates were similar for nighttime and 24-hour BP outcomes and for subgroup analyses of populations with HTN and resistant HTN.
[§] Study quality rating refers to quality of the SRs, not the quality of individual trials included by the reviews.
[ǁ] Study quality rating refers to quality of the SR, not the quality of individual trials included by the reviews.
[#] 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.

Abbreviations: AHI=apnea-hypopnea index; AUC=area under the curve; BMI=body mass index; BP=blood pressure; BQ=Berlin Questionnaire; CBV=cerebrovascular; CI=confidence interval; CV=cardiovascular; DBP=diastolic blood pressure; DM2=type 2 diabetes; ESS=Epworth Sleepiness Scale; EQ-5D=European Quality of Life Scale; FOSQ=Functional Outcomes of Sleep Questionnaire; HST=home sleep testing; HTN=hypertension; KQ=key question; MAD=mandibular advancement device; MCS=mental component summary score; mod=moderate; MVA=motor vehicle accident; MVAP=Multivariable Apnea Prediction; NR=not reported; OSA=obstructive sleep apnea; OSAS=obstructive sleep apnea syndrome; PAP=positive airway pressure; PCS=physical component summary score; PSG=polysomnography; QOL=quality of life; QSQ=Quebec Sleep Questionnaire; 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; SMD=standardized mean difference; Sn=sensitivity; Sp=specificity; SR=systematic review; vs.=versus.

Appendix A Table 1. Classification of Monitors Used for Diagnosis of OSA*

Type	Portability	Number of Channels (i.e., Physiologic Measures)	Typical Parameters	≥2 Airflow or Effort Channels	Measures AHI
I	Facility based	≥7 (usually 12–16)	EEG, EOG, EMG, ECG/HR, airflow (nasal 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 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 does not qualify as type III§	No	No

* Modified, with permission, from a previous systematic review;[47] personal communication with Dr. Ethan Balk (October 5, 2015).

† HR is allowed in place of ECG in type II portable monitors (PMs). Type II PMs 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, airflow, or both.

§ Parameters that are more commonly measured by type IV PMs include but are not limited to snoring, body position, leg movement, peripheral arterial tone, and plethysmography.

Abbreviations: AHI=apnea-hypopnea index; ECG=electrocardiogram; EEG=electroencephalogram; EMG=electromyogram; EOG=electrooculogram; HR=heart rate; OSA=obstructive sleep apnea; PM=portable monitor; SaO_2=arterial oxygen saturation.

Appendix A Table 2. Summary of Treatment Guidelines From Other Groups

Group, Year	Recommendations
American College of Physicians (ACP), 2013[96]	• 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) • MADs as an alternative therapy to CPAP treatment for patients diagnosed with OSA who prefer MADs or for those with adverse effects associated with CPAP treatment. (weak recommendation, low-quality evidence)
American Academy of Sleep Medicine (AASM), 2015 (Oral Appliances),[254] 2019 (PAP Treatment)[95]	• Clinicians should use PAP compared with no therapy to treat OSA in adults with excessive sleepiness (strong recommendation) and suggest use of PAP compared with no therapy to treat adults with comorbid hypertension and those with impaired sleep-related quality of life. (conditional recommendation) • PAP therapy should be initiated using either APAP at home or in-laboratory PAP titration in adults with OSA and no significant comorbidities and should use either CPAP or APAP for ongoing treatment of OSA in adults. (strong recommendation) • Clinicians should consider use of CPAP or APAP over BPAP in the routine treatment of OSA in adults. (conditional recommendation) • Clinicians should provide educational interventions with initiation of PAP therapy in adults with OSA. (strong recommendation) • Clinicians should consider implementing behavioral or troubleshooting interventions during the initial period of PAP therapy in adults with OSA. (conditional recommendation) • Sleep clinicians should consider providing a prescription for an oral appliance vs. no treatment for adult patients with OSA who are intolerant of CPAP therapy or who prefer alternative therapies (benefits clearly outweigh risks, high-quality evidence)
National Institute for Health and Clinical Excellence (NICE), 2008[255]	• Recommends CPAP as a treatment option for adults with moderate or severe symptomatic OSAHS. • Recommends CPAP as a treatment option for adults with mild OSAHS only if they have symptoms that affect their quality of life and their ability to perform their daily activities and only if lifestyle advice and 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.
U.S. Department of Veterans Affairs and the Department of Defense (VA/DoD), 2019[103]	• For patients with severe OSA (i.e., AHI >30 events/hour), the recommended initial therapy is PAP. For patients with mild to moderate OSA (i.e., AHI 5 to <30 events/hour), either PAP or MAD therapy can be considered for initial therapy; choice of treatment should be based on clinical evaluation, comorbidities, and patient preference. • Educational, behavioral therapy, and supportive interventions should be offered to improve PAP adherence. Weight loss and a comprehensive lifestyle intervention program should be encouraged in all patients with OSA who are overweight or obese; although weight loss alone is typically insufficient as therapy for OSA, weight loss may improve AHI. • In OSA patients who are not adherent to PAP or MAD therapy or who have persistent symptoms despite adequate therapy, referral to a clinician with expertise in sleep medicine is recommended.

Abbreviations: AASM=American Academy of Sleep Medicine; ACP=American College of Physicians; AHI=apnea-hypopnea index; APAP=auto-adjusting positive airway pressure; BPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; MAD=mandibular advancement device; NICE=National Institute for Health and Clinical Excellence; OSA=obstructive sleep apnea; OSAHS=obstructive sleep apnea-hypopnea syndrome; PAP=positive airway pressure; VA/DoD=U.S. Department of Veterans Affairs and the U.S. Department of Defense.

Appendix A Table 3. Summary of Screening Guidelines From Other Groups

Group, Year	Recommendations
American College of Physicians (ACP), 2014[226]	• A sleep study is recommended for patients with unexplained daytime sleepiness. (weak recommendation, low-quality evidence) • Polysomnography is recommended for diagnostic testing in patients with suspected OSA. Portable sleep monitors are recommended in patients without serious comorbidities as an alternative to polysomnography when polysomnography is not available for diagnostic testing. (weak recommendation, moderate-quality evidence)
Society of Anesthesia and Sleep Medicine (SASM), 2016[256]	• Adult patients at risk for OSA should be identified before surgery (Level of Evidence: Low; Grade of Recommendation: Weak for). • Screening tools such as STOP-BANG, P-SAP, Berlin Questionnaire, and ASA Check List can be used as preoperative screening tools to identify patients with suspected OSA (Level of Evidence: Moderate; Grade of Recommendation: Strong for). • There is insufficient evidence to support canceling or delaying surgery to perform more advanced screening techniques or sleep testing to diagnose OSA in those patients identified as being at high risk of OSA preoperatively, unless there is evidence of an associated significant or uncontrolled systemic disease or additional problems with ventilation or gas exchange (Level of Evidence: Low; Grade of Recommendation: Weak for).
American Academy of Sleep Medicine (AASM), 2017[6, 257]	• Clinical tools, questionnaires, and prediction algorithms should not be used to diagnose OSA in adults in the absence of PSG or in-home sleep apnea testing. (strong recommendation) • A home sleep apnea test (HSAT) should not be used for the general screening of populations who are asymptomatic. The need for and appropriateness of an HSAT to diagnose OSA or evaluate treatment efficacy must be based on the patient's medical history and an examination by a medical provider (face-to-face or via telemedicine). (medical position statement) • Diagnosis of OSA in uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA can be made with either PSG or in-home sleep apnea testing with a technically adequate device. If a single HSAT is negative, inconclusive, or technically inadequate, PSG should be performed for diagnosis. (strong recommendation) • PSG vs. in-home sleep apnea testing should be used for the diagnosis of OSA in patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular conditions, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid medication use, history of stroke, or severe insomnia. (strong recommendation)
National Institute for Health and Clinical Excellence (NICE), 2008[255]	• 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. • Moderate to severe OSAHS can be diagnosed from the patient's medical history and a sleep study using oximetry or other monitoring devices carried out in the patient'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. • Guidelines related to initial assessment and diagnosis are being developed (expected publication April 2021).[258]
U.S. Department of Veterans Affairs and the U.S. Department of Defense (VA/DoD), 2019[103]	• For patients who report sleep complaints, suggest using the STOP Questionnaire to stratify the risk of OSA. Consider assessing for sleep-disordered breathing in patients with a history of cardiovascular or cerebrovascular events, congestive heart failure, and chronic opioid use. (strength of recommendations: weak) • Among patients with a high pretest probability of OSA, suggest using a manually scored type II HSAT (unattended portable monitor) using an event index of ≥15 events per hour to establish diagnosis of moderate to severe OSA. (strength of recommendations: weak)

Abbreviations: AASM=American Academy of Sleep Medicine; ACP=American College of Physicians; ASA=American Society of Anesthesiologists; HSAT=home sleep apnea test; NICE=National Institute for Health and Clinical Excellence; OSA=obstructive sleep apnea; OSAHS=obstructive sleep apnea-hypopnea syndrome; P-SAP=perioperative sleep apnea prediction; PSG=polysomnography; SASM=Society of Anesthesia and Sleep Medicine; STOP-BANG=Snoring, Tiredness, Observed apnea, blood Pressure Questionnaire plus BMI, Age, Neck circumference, and Gender; VA/DoD=U.S. Department of Veterans Affairs and the U.S. Department of Defense.

CQ 1. 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?

Identifying and removing barriers to OSA diagnosis continues to be a challenge in the effort to address the disease. Barriers to diagnosis come from multiple aspects of the healthcare system, and many of these obstacles are external to the health care system itself. Following is a summary of the evidence surrounding the barriers to OSA diagnosis and some of measures that have been proposed to address these barriers.

Some studies have examined whether patients followed up with sleep labs after they were referred and—if not—the reasons why they did not follow up. The reasons found for lack of followup include misconceptions about OSA,[259, 260] work responsibilities,[259] negative views of OSA services,[259] and financial and transportation difficulties.[259] Some misconceptions involve a lack of understanding of the seriousness of the disease, such as conflating snoring with OSA.[259] Another study that included a large insurer's administrative data on more than 51,000 patients preauthorized for sleep testing found that patients with signs and symptoms of OSA such as snoring or gasping and sleepiness were more likely to be adherent to sleep testing than patients without such signs and symptoms.[261]

One study described a quality improvement project aimed at identifying barriers to OSA diagnosis that providers and patients faced in an internal medicine clinic in Buffalo, New York.[262] Among providers, barriers included a lack of knowledge about guidelines and OSA diagnosis, a lack of reminders to screen, and the extra time needed to use screening tools. Despite employing the STOP-BANG Questionnaire in patients with hypertension, physicians could not always document the results from paper questionnaires in the electronic health record. For patients, barriers to diagnosis include their lack of knowledge about OSA, lack of transportation to sleep clinics, and lack of health insurance and the inability to pay for sleep studies.

Other studies have supported the following barriers among providers: difficulty recognizing OSA symptoms,[263, 264] lack of time or reminders to screen for OSA during an appointment,[265, 266] delays in diagnostic testing,[264, 267] and under-referral to specialists for OSA diagnosis.[264] Multiple studies have also supported the idea that their lack of knowledge about OSA has prevented patients from disclosing their symptoms.[262, 264]

Efforts to make diagnosis more accessible are underway, but these solutions will come with tradeoffs. In-home PSG may address the transportation barriers and financial obstacles to diagnosing OSA.[259, 268-270] Despite the convenience of in-home PSG, the conclusion from one technical review of 50 commercial PMs and 25 research procedures used with adults indicates that PMs are appropriate for an initial OSA diagnosis.[271] The authors found that the sensitivity of the commercial devices was high, ranging from 60 to 100 percent, with a median of 93 percent, but that the median specificity was much lower (75%), ranging from 40 to 100 percent. Moreover, it was not clear whether all studies used PSG as the reference measure. One study included in the review that did use PSG to validate portable monitoring[272] found excellent

sensitivity with in-home portable monitoring in comparison with PSG, ranging from 92 percent (for AHI ≥15) to 96 percent (for AHI ≥5); specificity was lower, ranging from 43 to 77 percent. Therefore, providers should consider the limitations of portable monitoring when employing this method.

Finally, many structural barriers continue to prevent patients from being diagnosed with OSA. Finances,[259] geographical distance from specialists and sleep study centers,[268, 269] and provider inexperience[264] all appear to play a significant role in the underdiagnosis of OSA. These barriers are not distributed evenly, and it is likely that a significant portion of population affected by OSA in the United States is underdiagnosed due to these diagnostic obstacles. Direct evidence of diagnostic obstacles remains scarce; therefore, we recommend that more studies investigate this issue.

CQ 2. Is There an Association Between AHI and Health Outcomes?

The apnea-hypopnea index (AHI) is often used to indicate the severity of OSA and represents the number of apnea and hypopnea events per hour of sleep. According to the American Academy of Sleep Medicine classification, having fewer than 5 AHI events per hour is considered normal, having 5 to 15 AHI events per hour is considered mild OSA, having 15 to 29 AHI events per hour is considered moderate OSA, and 30 or more AHI events per hour is considered severe OSA.[273]

In the previous USPSTF review on this topic (published in 2017), we summarized 11 prospective cohort studies (26,954 total participants) that compared participants with OSA to those without OSA or to those with varying degrees of OSA who were untreated for OSA.[92] The review found that severe (AHI ≥30) OSA or moderate to severe (AHI ≥15) OSA was associated with an increased risk of all-cause mortality (pooled HR, 2.07 [95% CI, 1.48 to 2.91]; followup ranged from 3.4 to 20 years) and cardiovascular (CV) mortality (data not pooled). The review reported that studies assessing whether moderate (AHI 15 to <30) or mild (AHI 5 to <15) OSA levels are associated with mortality did not find a statistically significant association. The review noted that included studies controlled for multiple potential confounders, but that residual confounding attributable to health-related factors (such as physical activity or diet) was possible and generally not accounted for. A single study was available for each other outcome (i.e., cancer-related mortality, nonfatal CV events, heart failure, coronary heart disease, stroke, cognitive impairment or dementia, and cognitive decline), for which findings were imprecise, consistency was unknown (single study for each), and evidence was limited by risk of bias, especially from potential residual confounding.[92]

More recent systematic reviews (SRs) of these outcomes describe similar findings.[274-280] These reviews are often framed as investigating the relationship between OSA and a given health outcome; however, OSA is typically measured by AHI and usually following the American Academy of Sleep Medicine classification. These SRs rely largely on prospective and occasionally retrospective cohort studies (that generally have a higher risk of bias, and therefore were not eligible for the 2017 review conducted for the USPSTF) of untreated individuals. Comparison groups vary and include persons with no OSA (AHI <5) or persons with less severe

OSA (AHI ranging from 5 to <30). Additionally, most studies included in these reviews were comprised of predominantly male participants.

A 2017 SR considered the relationship between the various levels of OSA severity (measured by AHI) and CV and mortality outcomes.[274] This review included 16 studies (24,308 total participants) that were published through May 2016 with followup ranging from 2.9 to 18.0 years. Meta-analyses of relevant studies found that severe OSA (AHI ≥30) was associated with increased risk of major CV events (relative risk [RR], 2.04 [95% CI, 1.56 to 2.66]; p<0.001), coronary heart disease (RR, 1.63 [95% CI, 1.18 to 2.26]; p=0.003), stroke (RR, 2.15 [95% CI, 1.42 to 3.24]; p<0.001), cardiac death (RR, 2.96 [95% CI, 1.45 to 6.01]; p=0.003), and all-cause mortality (RR, 1.54 [95% CI, 1.21 to 1.97]; p<0.001), but not heart failure (RR, 1.44 [95% CI, 0.94 to 2.21]; p=0.097). Mild OSA was not significantly associated with increased risk of any of these outcomes and moderate OSA was associated only with increased risk of major CV events (RR, 1.16 [95% CI, 1.01 to 1.33]; p=0.034) and coronary heart disease (RR, 1.38 [95% CI, 1.04 to 1.83]; p=0.026). Several older SRs and meta-analyses, including many of the same primary studies, have found qualitatively similar results indicating that severe OSA is associated with increased risk of many CV and mortality outcomes while mild and moderate often are not.[275-278]

Additional SRs and meta-analyses have considered other important outcomes. In a 2017 meta-analysis of six studies, sleep-disordered breathing was associated with increased odds of cognitive impairment, including "clinically relevant cognitive decline or risk of dementia" (OR, 1.26 [95% CI, 1.05 to 1.50]; p=0.01).[280] It should be noted that only four of these six studies defined sleep-disordered breathing using AHI; the other two used a clinical diagnosis. A separate 2018 meta-analysis estimated an increased risk of atrial fibrillation with any sleep apnea-hypopnea syndrome (RR, 1.7 [95% CI, 1.53 to 1.89]; p=NR).[279] Using a subset of studies that provided associations by OSA severity, having mild, moderate, and severe OSA were all associated with having an increased risk of atrial fibrillation with increasing magnitudes (mild RR, 1.52 [95% CI, 1.28 to 1.79]; p=0.01; moderate RR, 1.88 [95% CI, 1.55 to 2.27]; p=0.017; severe RR, 2.16 [95% CI, 1.78 to 2.62]; p<0.001).

Importantly, secondary meta-analyses by gender often identified a similar association between severe OSA and significantly increased risk of CV and mortality for men,[274, 276] but not for women. Although analyses of men largely drove the overall findings, no significant difference was found between men and women. Authors suggest that this may be due to the higher prevalence of OSA among men, biologic differences between the sexes, and most studies considering only or at least predominantly men.[274]

Overall, meta-analyses suggest that severe OSA (AHI ≥30) is associated with an increased risk of many adverse health outcomes, including CV events, mortality, and cognitive impairment. Some studies suggest that the risk of such outcomes increases with each level of OSA severity, which may indicate a dose-response effect; however, this finding is not consistent across all studies or outcomes. Lastly, findings of increased risk associated with severe OSA are the strongest among male populations; however, it is difficult to assess if these relationships do not hold for female populations or if it is due to more sparse evidence on female populations.

Appendix B1. Original Search Strategies

PubMed, Interventions, 1-3-2021

Search Number	Query	Filters	Results
1	"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]		45,620
2	"Continuous Positive Airway Pressure"[Mesh] OR "Intermittent Positive-Pressure Ventilation"[MeSH] OR "Mandibular Advancement/instrumentation"[Mesh] OR "Mandibular Prosthesis"[MeSH Terms] OR "Positive-Pressure Respiration"[Mesh:NoExp]		27,441
3	"Biphasic Intermittent Positive Airway Pressure"[tw] OR BiPAP[tw] OR "Continuous Positive Airway Pressure"[tw] OR CPAP[tw] OR "IPPV"[tw] OR "Inspiratory Positive-Pressure Ventilation"[tw] OR "Inspiratory Positive Pressure Ventilation"[tw] OR "Intermittent Positive Pressure Ventilation"[tw] OR "mandibular advancement device"[tw] OR "mandibular advancement devices"[tw] OR "oral appliance"[tw] OR "oral appliances"[tw] OR PAP[tiab]		39,066
4	#1 AND (#2 OR #3)		10,423
5	#1 AND (#2 OR #3)	English	9,124
6	(#5 AND Humans[Mesh:NOEXP]) OR (#5 NOT Animals[Mesh:NOEXP])		9,097
7	#6 AND ("2015/04/01"[Date - Publication] : "3000"[Date - Publication])		3,341
8	#6 AND ("2015/04/01"[Date - Publication] : "3000"[Date - Publication])	Adult: 19+ years	1,485
9	#7 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)		2,639
10	#8 OR #9		2,944
11	(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 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 Interactive Tutorial[Publication Type] OR Interview[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 Periodical Index[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type])		4,306,169
12	#10 NOT #11		2,469
13	("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "Systematic Reviews as Topic"[Mesh] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab] OR "Umbrella Review"[tiab]		352,518
14	#12 AND #13		225
15	((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])		808,286
16	#12 AND #15		373
17	#16 NOT #14		349

Appendix B1. Original Search Strategies

PubMed, Screening, 1-3-2021

Search Number	Query	Filters	Results
1	"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]		45,620
2	"Body Mass Index"[Mesh] OR "Body Weight"[Mesh] OR "Decision Support Techniques"[Mesh] OR "Obesity"[Mesh] OR Psychometrics[Mesh] OR "Snoring"[Mesh] OR "Surveys and Questionnaires"[Mesh] OR instrument[tiab] OR instruments[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR scale[tiab] OR scales[tiab]		2,680,695
3	Oximetry[MeSH] OR "Berlin Questionnaire" OR "Clinical prediction tool*" OR "Clinical prediction rule*" OR "Clinical prediction score*" OR "Craniofacial structure*" OR "Epworth Sleepiness Scale" OR Mallampati OR "Multivariable Apnea Prediction Index" OR "Multivariable Apnoea Prediction Index" OR NAMES OR "Neck circumference" OR "Nocturnal choking" OR "Nocturnal gasping" OR oximetry OR oximetries OR "oxygen desaturation" OR photoplethysmography OR "Sleep Apnea Clinical Score" OR snoring OR "Snoring Scale" OR sleepiness OR "STOP-BAG" OR "STOP-Bang" OR "STOP Questionnaire" OR "Wisconsin Sleep Questionnaire"		181,693
4	#1 AND #2		17,390
5	#1 AND #3		13,398
6	"Diagnostic Tests, Routine"[Mesh] OR "False Negative Reactions"[Mesh] OR "False Positive Reactions"[Mesh] OR "Mass Screening"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "ROC Curve"[Mesh] OR "Diagnosis"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR accuracy[tw] OR diagno*[tw] OR "false positive"[tw] OR "false negative"[tw] OR "likelihood ratio"[tw] OR "predictive value"[tw] OR reproducib*[tw] OR ROC[tw] OR screen[tw] OR screening[tiab] OR sensitivity[tw] OR specificity[tw]		12,030,098
7	#4 AND #6		15,039
8	#5 OR #7		21,063
9	#5 OR #7	English	18,780
10	(#9 AND Humans[Mesh:NOEXP]) OR (#9 NOT Animals[Mesh:NOEXP])		18,651
11	#10 AND ("2015/04/01"[Date - Publication] : "3000"[Date - Publication])		6,485
12	#10 AND ("2015/04/01"[Date - Publication] : "3000"[Date - Publication])	Adult: 19+ years	3,458
13	#11 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)		4,085
14	#12 OR #13		5,114
15	(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 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 Interactive Tutorial[Publication Type] OR Interview[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 Periodical Index[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type])		4,306,169
16	#14 NOT #15		4,783
17	((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])		808,286
18	#16 AND #17		387

Appendix B1. Original Search Strategies

Search Number	Query	Filters	Results
19	"Prospective Studies"[Mesh] OR "Cross-Sectional Studies"[MeSH] OR (prospective[tw] AND cohort[tw]) OR "cross-section*"[tw] OR "cross section*"[tw] OR prognostic*[tiab] OR prospectively[tiab]		1,481,555
20	#16 AND #19		1,364
21	#20 NOT #18		1,270

PubMed, CQ 1 Search (Barriers to Screening), 1-3-2021

Search Number	Query	Filters	Results
1	"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]		45,620
2	"Surveys and Questionnaires"[Mesh] OR ("Mass Screening"[Mesh] OR screening[tiab]) OR "Predictive Value of Tests"[Mesh] OR ("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]) OR ("Neck circumference"[All Fields] OR Mallampati OR "Nocturnal choking"[All Fields] OR "Nocturnal gasping"[All Fields] OR ("Body Mass Index"[Mesh]) OR "Body Weight"[Mesh] OR "Obesity"[Mesh]) OR "Snoring"[Mesh] OR snoring OR Sleepiness)		12,493,985
3	#1 AND #2		35,821
4	#1 AND ("Decision Support Techniques"[Mesh] OR "Clinical prediction tool*" OR "Clinical prediction rule*" OR "Clinical prediction score*")		183
5	"Epworth Sleepiness Scale"[All Fields] OR "STOP Questionnaire"[All Fields] OR "STOP-BAG"[All Fields] OR "STOP-Bang"[All Fields] OR "Berlin Questionnaire"[All Fields] OR "Wisconsin Sleep Questionnaire"[All Fields] OR "Multivariable Apnea Prediction Index"[All Fields] OR "Multivariable Apnoea Prediction Index"[All Fields] OR "Snoring Scale"[All Fields] OR "Sleep Apnea Clinical Score"[All Fields]		4,980
6	Photoplethysmography		3,217
7	#3 OR #4 OR #5 OR #6		41,038
8	"Focus Groups"[MeSH Terms] OR "Grounded Theory"[MeSH Terms] OR "Interviews as Topic"[MeSH Terms] OR "Qualitative Research"[MeSH Terms] OR "attitudes"[Title/Abstract] OR "barrier*"[Title/Abstract] OR "facilitators"[Title/Abstract] OR "experiences"[Title/Abstract] OR "perceptions"[Title/Abstract] OR "perspectives"[Title/Abstract] OR "preferences"[Title/Abstract] OR "values"[Title/Abstract] OR "viewpoints"[Title/Abstract] OR "views"[Title/Abstract] OR "critical interpretive"[Title/Abstract] OR "critical race"[Title/Abstract] OR "critical realism"[Title/Abstract] OR "critical realist"[Title/Abstract] OR "ethnograph*"[Title/Abstract] OR "Grounded Theory"[Title/Abstract] OR "phenomenolog*"[Title/Abstract] OR "case study"[Title/Abstract] OR "content analysis"[Title/Abstract] OR "descriptive"[Title/Abstract] OR "focus group"[Title/Abstract] OR "Focus Groups"[Title/Abstract] OR "interview*"[Title/Abstract] OR "mixed design"[Title/Abstract] OR "mixed methods"[Title/Abstract] OR "qualitative"[Title/Abstract]		2,575,962
9	#7 AND #8		4,493
10	#7 AND #8	Humans	3,934
11	#7 AND #8	Humans, English	3,588

Appendix B1. Original Search Strategies

Search Number	Query	Filters	Results
12	#7 AND #8	in the last 10 years, Humans, English	2,126
13	barrier*[tiab]		312,282
14	#9 AND #13		156

PubMed, CQ 2 Search (AHI), 1-3-2021

Search Number	Query	Filters	Results
1	"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]		45,620
2	"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]		9,102
3	#1 AND #2		8,777
4	"Cardiovascular Diseases"[Mesh] OR "Cerebrovascular Disorders"[Mesh] OR "Cognition Disorders"[Mesh] OR "Fatal Outcome"[Mesh] OR "Headache"[Mesh] OR "Cognitive Dysfunction"[Mesh] OR "Mortality"[Mesh] OR "mortality" [Subheading] OR "Motor Vehicles"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Patient Outcome Assessment"[Mesh] OR "Outcome Assessment, Health Care"[Mesh] OR "Quality of Life"[Mesh] OR Stroke[Mesh]		4,092,611
5	cardiovascular*[tiab] OR cerebrovasc*[tiab] OR cognit*[tiab] OR headache[tiab] OR "heart failure"[tiab] OR mortality[tiab] OR "motor vehicle"[tiab] OR "motor vehicles"[tiab] OR outcome*[tiab] OR "quality of life"[tiab]		3,428,704
6	#4 OR #5		6,046,109
7	#3 AND #6		4,738
8	#3 AND #6	English	4,485
9	(#8 AND Humans[Mesh:NOEXP]) OR (#8 NOT Animals[Mesh:NOEXP])		4,480
10	#9 AND ("2015/04/01"[Date - Publication] : "3000"[Date - Publication])		2,121
11	#9 AND ("2015/04/01"[Date - Publication] : "3000"[Date - Publication])	Adult: 19+ years	1,322
12	#10 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)		1,389
13	#11 OR #12		1,740
14	(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 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 Interactive Tutorial[Publication Type] OR Interview[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 Periodical Index[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type])		4,306,169
15	#13 NOT #14		1,708
16	((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])		808,286
17	#15 AND #16		229

Appendix B1. Original Search Strategies

Cochrane Library, Interventions, 1-11-2021

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] OR [mh "Sleep Apnea, Obstructive"] OR "Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea" OR "Obstructive Sleep Apnoea" OR "Obstructive Sleep Apnoeas" OR OSAHS OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"	6,781
#2	[mh "Continuous Positive Airway Pressure"] OR [mh "Intermittent Positive-Pressure Ventilation"] OR [mh "Mandibular Advancement"/IS] OR [mh "Mandibular Prosthesis"] OR [mh ^"Positive-Pressure Respiration"] OR BiPAP OR "Biphasic Intermittent Positive Airway Pressure" 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 "mandibular advancement device" OR "mandibular advancement devices" OR "oral appliance" OR "oral appliances" OR PAP:ti,ab	9,915
#3	#1 AND #2	3,266
#4	#3 NOT ([mh animals] NOT [mh humans])	3,266
#5	#4 NOT (Address:pt OR “autobiography”:pt OR “bibliography”:pt OR “biography”:pt OR “case control” OR "case report" OR “case reports” OR “case series” OR “comment”:pt OR "comment on" OR congress:pt OR “cross-sectional” OR “dictionary”:pt OR “directory”:pt OR “editorial”:pt OR “festschrift”:pt OR “historical article”:pt OR “interview”:pt OR lecture:pt OR "legal case":pt OR “legislation”:pt OR letter:pt OR “news”:pt OR “newspaper article”:pt OR “patient education handout”:pt OR “periodical index”:pt OR “retrospective cohort” OR ([mh "Animals"] NOT [mh "Humans"]) OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae)	3,147
#6	MeSH descriptor: [Adult] explode all trees	462,536
#7	#5 AND #6	888
#8	#5 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)	3,077
#9	#7 OR #8	3,081
#10	#9 with Cochrane Library publication date Between Apr 2015 and Jan 2021	1,971
#11	"randomized controlled trial":pt OR "randomized controlled trial as topic":pt OR "single-blind method":pt OR "double-blind method":pt OR "random allocation":pt	499,052
#12	#10 AND #11	294

Cochrane Library, Screening, 1-11-2021

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] OR [mh "Sleep Apnea, Obstructive"] OR "Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea" OR "Obstructive Sleep Apnoea" OR "Obstructive Sleep Apnoeas" OR OSAHS OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"	6,781
#2	[mh "Body Mass Index"] OR [mh "Body Weight"] OR [mh "Decision Support Techniques"] OR [mh "Obesity"] OR [mh Psychometrics] OR [mh "Snoring"] OR [mh "Surveys and Questionnaires"] OR instrument:ti,ab OR instruments:ti,ab OR questionnaire:ti,ab OR questionnaires:ti,ab OR scale:ti,ab OR scales:ti,ab	317,325
#3	[mh Oximetry] OR "Berlin Questionnaire" OR "Clinical prediction tool*" OR "Clinical prediction rule*" OR "Clinical prediction score*" OR "Craniofacial structure*" OR "Epworth Sleepiness Scale" OR Mallampati OR "Multivariable Apnea Prediction Index" OR "Multivariable Apnoea Prediction Index" OR NAMES OR "Neck circumference" OR "Nocturnal choking" OR "Nocturnal gasping" OR oximetry OR oximetries OR "oxygen desaturation" OR photoplethysmography OR "Sleep Apnea Clinical Score" OR snoring OR "Snoring Scale" OR sleepiness OR "STOP-BAG" OR "STOP-Bang" OR "STOP Questionnaire" OR "Wisconsin Sleep Questionnaire"	13,722
#4	#1 AND #2	2,304
#5	#1 AND #3	2,413
#6	[mh "Diagnosis"] OR [mh "Diagnostic Tests, Routine"] OR [mh "False Negative Reactions"] OR [mh "False Positive Reactions"] OR [mh "Mass Screening"] OR [mh "Predictive Value of Tests"] OR [mh "ROC Curve"] OR [mh "Reproducibility of Results"] OR [mh "Sensitivity and Specificity"] OR accuracy OR diagno* OR "false negative" OR "false positive" OR "likelihood ratio" OR "predictive value" OR ROC OR reproducib* OR screen OR screening OR sensitivity OR specificity	568,224
#7	#4 AND #6	1,490
#8	#5 OR #7	2,975
#9	#8 NOT ([mh animals] NOT [mh humans])	2,975

Appendix B1. Original Search Strategies

ID	Search	Hits
#10	#9 NOT (Address:pt OR “autobiography”:pt OR “bibliography”:pt OR “biography”:pt OR “case control” OR "case report" OR “case reports” OR “case series” OR “comment”:pt OR "comment on" OR congress:pt OR “cross-sectional” OR “dictionary”:pt OR “directory”:pt OR “editorial”:pt OR “festschrift”:pt OR “historical article”:pt OR “interview”:pt OR lecture:pt OR "legal case":pt OR “legislation”:pt OR letter:pt OR “news”:pt OR “newspaper article”:pt OR “patient education handout”:pt OR “periodical index”:pt OR “retrospective cohort” OR ([mh "Animals"] NOT [mh "Humans"]) OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae)	2,831
#11	MeSH descriptor: [Adult] explode all trees	462,536
#12	#10 AND #11	1,023
#13	#12 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)	1,010
#14	#12 OR #13	1,023
#15	#14 with Cochrane Library publication date Between Apr 2015 and Jan 2021	338
#16	#15 AND ("randomized controlled trial":pt OR "randomized controlled trial as topic":pt OR "single-blind method":pt OR "double-blind method":pt OR "random allocation":pt)	312
#17	#15 AND ([mh "Prospective Studies"] OR [mh "Cross-Sectional Studies"] OR (prospective AND cohort) OR "cross-section*" OR "cross section*" OR prognostic*:ti,ab OR prospectively:ti,ab)	88
#18	#17 NOT #16	11

Embase, Interventions, 1-4-2021

Query	Search	Results
#1	‘obstructive sleep apneas’ OR ’obstructive sleep apnea’/exp OR ’obstructive sleep apnea’ OR ’obstructive sleep apnea syndrome’/exp OR ’obstructive sleep apnea syndrome’ OR ’obstructive sleep apnoeas’ OR ’obstructive sleep apnoea’/exp OR ’obstructive sleep apnoea’ OR osahs OR ((‘sleep apnea’/exp OR ’sleep apnea’) AND (‘hypopnea’/exp OR hypopnea)) OR ’sleep apnea syndromes’/exp OR ’sleep apnea syndromes’ OR ’sleep disordered breathing’/exp OR ’sleep disordered breathing’	86,778
#2	‘continuous positive airway pressure’/exp OR ’cpap device’/exp OR ’intermittent positive pressure ventilation’/exp OR ’mandible prosthesis’/exp OR ’positive end expiratory pressure’/exp/mj OR ’positive pressure ventilation’/exp OR bipap OR ’biphasic intermittent positive airway pressure’ 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 ’mandibular advancement device’ OR ’mandibular advancement devices’ OR ’oral appliance’ OR ’oral appliances’ OR pap:ti,ab	97,199
#3	#1 AND #2	21,371
#4	#3 AND [humans]/lim	20,299
#5	#4 NOT ([editorial]/lim OR [letter]/lim OR [note]/lim)	18,156
#6	#5 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	9,184
#7	#5 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)	16,252
#8	#6 OR #7	16,739
#9	#8 AND [1-4-2015]/sd NOT [5-1-2021]/sd	7,768
#10	‘systematic review’/exp OR ’systematic review (topic)’/exp OR ’meta analysis’/exp OR ’meta analysis (topic)’/exp OR ’systematic literature review’:ti,ab OR ’this systematic review’:ti,ab OR ’umbrella review’:ti,ab OR ’meta-analysis’:ti,ab OR ’meta-analyses’:ti,ab OR ’meta-synthesis’:ti,ab OR ’meta-syntheses’:ti,ab	479,075
#11	#9 AND #10	503
#12	#9 AND #10 AND ([medline]/lim OR [pubmed-not-medline]/lim)	309
#13	#11 NOT #12	194
#14	‘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)	8,239,855
#15	#9 AND #14	3,023
#16	#15 AND ([medline]/lim OR [pubmed-not-medline]/lim)	1,222
#17	#15 NOT #16	1,801
#18	#17 NOT #13	1,742

Appendix B1. Original Search Strategies

Embase, Screening, 1-4-2021

Query	Search	Results
#1	'sleep disordered breathing'/exp OR 'obstructive sleep apneas' OR 'obstructive sleep apnea' OR 'obstructive sleep apnea syndrome' OR 'obstructive sleep apnoeas' OR 'obstructive sleep apnoea' OR osahs OR ('sleep apnea' AND hypopnea) OR 'sleep apnea syndromes' OR 'sleep disordered breathing'	86,787
#2	'body mass'/exp OR 'body weight'/exp OR 'decision support system'/exp OR 'obesity'/exp OR 'psychometry'/exp OR 'snoring'/exp OR 'questionnaire'/exp OR instrument:ti,ab OR instruments:ti,ab OR questionnaire:ti,ab OR questionnaires:ti,ab OR scale:ti,ab OR scales:ti,ab	3,401,355
#3	'pulse oximetry'/exp OR 'berlin questionnaire' OR 'clinical prediction tool*' OR 'clinical prediction rule*' OR 'clinical prediction score*' OR 'craniofacial structure*' OR 'epworth sleepiness scale' OR mallampati OR 'multivariable apnea prediction index' OR 'multivariable apnoea prediction index' OR names OR 'neck circumference' OR 'nocturnal choking' OR 'nocturnal gasping' OR oximetry OR oximetries OR 'oxygen desaturation' OR photoplethysmography OR 'sleep apnea clinical score' OR snoring OR 'snoring scale' OR sleepiness OR 'stop-bag' OR 'stop-bang' OR 'stop questionnaire' OR 'wisconsin sleep questionnaire'	112,230
#4	#1 AND #2	42,692
#5	#1 AND #3	27,114
#6	'diagnosis'/exp OR 'diagnostic test'/exp OR 'false negative result'/exp OR 'false positive result'/exp OR 'mass screening'/exp OR 'predictive value'/exp OR 'receiver operating characteristic'/exp OR 'reproducibility'/exp OR 'sensitivity and specificity'/exp OR accuracy OR diagno* OR 'false negative' OR 'false positive' OR 'likelihood ratio' OR 'predictive value' OR roc OR reproducib* OR screen OR screening OR sensitivity OR specificity	12,134,617
#7	#4 AND #6	24,647
#8	#5 OR #7	39,206
#9	#8 AND [humans]/lim	37,067
#10	#9 NOT ([editorial]/lim OR [letter]/lim OR [note]/lim)	35,141
#11	#10 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	19,843
#12	#10 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)	28,894
#13	#11 OR #12	30,435
#14	#13 AND [1-4-2015]/sd NOT [5-1-2021]/sd	15,282
#15	#14 AND ([medline]/lim OR [pubmed-not-medline]/lim)	6,566
#16	#14 NOT #15	8,716
#17	'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)	8,239,855
#18	#16 AND #17	4,055
#19	#18 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	589
#20	'cohort analysis'/exp OR 'epidemiological study' OR (cohort AND (study OR studies)) OR 'prospective study'/exp OR (prospective* AND cohort) OR 'cross-section*' OR 'cross section*' OR prognostic*:ti,ab OR prospectively:ti,ab	2,648,370
#21	#16 AND #20	2,519
#22	#21 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	463
#23	#22 NOT #19	237

EMBASE, Screening Bridge Search to include Emtree term "photoelectric plethysmography", 1-6-2021

Query	Search	Results
#1	'obstructive sleep apneas' OR 'obstructive sleep apnea'/exp OR 'obstructive sleep apnea' OR 'obstructive sleep apnea syndrome'/exp OR 'obstructive sleep apnea syndrome' OR 'obstructive sleep apnoeas' OR 'obstructive sleep apnoea'/exp OR 'obstructive sleep apnoea' OR osahs OR (('sleep apnea'/exp OR 'sleep apnea') AND ('hypopnea'/exp OR hypopnea)) OR 'sleep apnea syndromes'/exp OR 'sleep apnea syndromes' OR 'sleep disordered breathing'/exp OR 'sleep disordered breathing'	87,021
#2	'photoelectric plethysmography'/exp NOT photoplethysmography	1,706
#3	#1 AND #2	50
#4	#3 AND [humans]/lim	49

Appendix B1. Original Search Strategies

Query	Search	Results
#5	#4 NOT ([editorial]/lim OR [letter]/lim OR [note]/lim)	46
#6	#5 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	24
#7	#5 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)	33
#8	#6 OR #7	34
#9	#8 AND [1-4-2015]/sd NOT [5-1-2021]/sd	22
#10	#9 AND ([medline]/lim OR [pubmed-not-medline]/lim)	13
#11	#9 NOT #10	9
#12	'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)	8,245,186
#13	#11 AND #12	2
#14	#13 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	2
#15	'cohort analysis'/exp OR 'epidemiological study' OR (cohort AND (study OR studies)) OR 'prospective study'/exp OR (prospective* AND cohort) OR 'cross-section*' OR 'cross section*' OR prognostic*:ti,ab OR prospectively:ti,ab	2,650,467
#16	#11 AND #15	2
#17	#16 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	2
#18	#17 NOT #14	1

PubMed, Interventions, 8-22-2021

Search Number	Query	Filters	Results
1	"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]		47,885
2	"Continuous Positive Airway Pressure"[Mesh] OR "Intermittent Positive-Pressure Ventilation"[MeSH] OR "Mandibular Advancement/instrumentation"[Mesh] OR "Mandibular Prosthesis"[MeSH Terms] OR "Positive-Pressure Respiration"[Mesh:NoExp]		28,331
3	"Biphasic Intermittent Positive Airway Pressure"[tw] OR BiPAP[tw] OR "Continuous Positive Airway Pressure"[tw] OR CPAP[tw] OR "IPPV"[tw] OR "Inspiratory Positive-Pressure Ventilation"[tw] OR "Inspiratory Positive Pressure Ventilation"[tw] OR "Intermittent Positive Pressure Ventilation"[tw] OR "mandibular advancement device"[tw] OR "mandibular advancement devices"[tw] OR "oral appliance"[tw] OR "oral appliances"[tw] OR PAP[tiab]		40,452
4	#1 AND (#2 OR #3)		10,915
5	#1 AND (#2 OR #3)	English	9,602
6	(#5 AND Humans[Mesh:NOEXP]) OR (#5 NOT Animals[Mesh:NOEXP])		9,572
7	#6 AND ("2020/07/03"[Date - Publication] : "3000"[Date - Publication])		829
8	#6 AND ("2020/07/03"[Date - Publication] : "3000"[Date - Publication])	Adult: 19+ years	163
9	#7 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)		632
10	#8 OR #9		684
11	(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 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 Interactive Tutorial[Publication Type] OR Interview[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 Periodical Index[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type])		4,441,214
12	#10 NOT #11		623

Appendix B1. Original Search Strategies

Search Number	Query	Filters	Results
13	("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "Systematic Reviews as Topic"[Mesh] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab] OR "Umbrella Review"[tiab]		389,192
14	#12 AND #13		59
15	((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])		836,623
16	#12 AND #15		64
17	#16 NOT #14		58

PubMed, Screening, 8-22-2021

Search Number	Query	Filters	Results
1	"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]		47,885
2	"Body Mass Index"[Mesh] OR "Body Weight"[Mesh] OR "Decision Support Techniques"[Mesh] OR "Obesity"[Mesh] OR Psychometrics[Mesh] OR "Snoring"[Mesh] OR "Surveys and Questionnaires"[Mesh] OR instrument[tiab] OR instruments[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR scale[tiab] OR scales[tiab]		2,818,571
3	Oximetry[MeSH] OR "Berlin Questionnaire" OR "Clinical prediction tool*" OR "Clinical prediction rule*" OR "Clinical prediction score*" OR "Craniofacial structure*" OR "Epworth Sleepiness Scale" OR Mallampati OR "Multivariable Apnea Prediction Index" OR "Multivariable Apnoea Prediction Index" OR NAMES OR "Neck circumference" OR "Nocturnal choking" OR "Nocturnal gasping" OR oximetry OR oximetries OR "oxygen desaturation" OR photoplethysmography OR "Sleep Apnea Clinical Score" OR snoring OR "Snoring Scale" OR sleepiness OR "STOP-BAG" OR "STOP-Bang" OR "STOP Questionnaire" OR "Wisconsin Sleep Questionnaire"		191,735
4	#1 AND #2		18,243
5	#1 AND #3		14,026
6	"Diagnostic Tests, Routine"[Mesh] OR "False Negative Reactions"[Mesh] OR "False Positive Reactions"[Mesh] OR "Mass Screening"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "ROC Curve"[Mesh] OR "Diagnosis"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR accuracy[tw] OR diagno*[tw] OR "false positive"[tw] OR "false negative"[tw] OR "likelihood ratio"[tw] OR "predictive value"[tw] OR reproducib*[tw] OR ROC[tw] OR screen[tw] OR screening[tiab] OR sensitivity[tw] OR specificity[tw]		12,455,932
7	#4 AND #6		15,792
8	#5 OR #7		22,077
9	#5 OR #7	English	19,772
10	(#9 AND Humans[Mesh:NOEXP]) OR (#9 NOT Animals[Mesh:NOEXP])		19,640
11	#10 AND ("2020/07/03"[Date - Publication] : "3000"[Date - Publication])		1,479
12	#10 AND ("2020/07/03"[Date - Publication] : "3000"[Date - Publication])	Adult: 19+ years	353
13	#11 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)		943
14	#12 OR #13		1,068

Appendix B1. Original Search Strategies

Search Number	Query	Filters	Results
15	(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 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 Interactive Tutorial[Publication Type] OR Interview[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 Periodical Index[Publication Type] OR Scientific Integrity Review[Publication Type] OR Video Audio Media[Publication Type])		4,441,245
16	#14 NOT #15		1,009
17	((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])		836,623
18	#16 AND #17		63
19	"Prospective Studies"[Mesh] OR "Cross-Sectional Studies"[MeSH] OR (prospective[tw] AND cohort[tw]) OR "cross-section*"[tw] OR "cross section*"[tw] OR prognostic*[tiab] OR prospectively[tiab]		1,578,546
20	#16 AND #19		239
21	#20 NOT #18		223

Cochrane Library, Interventions, 8-22-2021

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] OR [mh "Sleep Apnea, Obstructive"] OR "Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea" OR "Obstructive Sleep Apnoea" OR "Obstructive Sleep Apnoeas" OR OSAHS OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"	7,109
#2	[mh "Continuous Positive Airway Pressure"] OR [mh "Intermittent Positive-Pressure Ventilation"] OR [mh "Mandibular Advancement"/IS] OR [mh "Mandibular Prosthesis"] OR [mh ^"Positive-Pressure Respiration"] OR BiPAP OR "Biphasic Intermittent Positive Airway Pressure" 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 "mandibular advancement device" OR "mandibular advancement devices" OR "oral appliance" OR "oral appliances" OR PAP:ti,ab	10,302
#3	#1 AND #2	3,398
#4	#3 NOT ([mh animals] NOT [mh humans])	3,398
#5	#4 NOT (Address:pt OR “autobiography”:pt OR “bibliography”:pt OR “biography”:pt OR “case control” OR "case report" OR “case reports” OR “case series” OR “comment”:pt OR "comment on" OR congress:pt OR “cross-sectional” OR “dictionary”:pt OR “directory”:pt OR “editorial”:pt OR “festschrift”:pt OR “historical article”:pt OR “interview”:pt OR lecture:pt OR "legal case":pt OR “legislation”:pt OR letter:pt OR “news”:pt OR “newspaper article”:pt OR “patient education handout”:pt OR “periodical index”:pt OR “retrospective cohort” OR ([mh "Animals"] NOT [mh "Humans"]) OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae)	3,267
#6	[mh Adult]	476,600
#7	#5 AND #6	919
#8	#5 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)	3,195
#9	#7 OR #8	3,199
#10	#9 with Cochrane Library publication date Between Jul 2020 and Dec 2021	238
#11	"randomized controlled trial":pt OR "randomized controlled trial as topic":pt OR "single-blind method":pt OR "double-blind method":pt OR "random allocation":pt	518,722
#12	#10 AND #11	29
#13	#12 with Publication Year from 2020 to 2021, in Trials	25

Appendix B1. Original Search Strategies

Cochrane Library, Screening, 8-22-2021

ID	Search	Hits
#1	[mh "Sleep Apnea Syndromes"] OR [mh "Sleep Apnea, Obstructive"] OR "Obstructive Sleep Apneas" OR "Obstructive Sleep Apnea" OR "Obstructive Sleep Apnoea" OR "Obstructive Sleep Apnoeas" OR OSAHS OR ("sleep apnea" AND hypopnea) OR "sleep disordered breathing"	7,109
#2	[mh "Body Mass Index"] OR [mh "Body Weight"] OR [mh "Decision Support Techniques"] OR [mh "Obesity"] OR [mh Psychometrics] OR [mh "Snoring"] OR [mh "Surveys and Questionnaires"] OR instrument:ti,ab OR instruments:ti,ab OR questionnaire:ti,ab OR questionnaires:ti,ab OR scale:ti,ab OR scales:ti,ab	336,819
#3	[mh Oximetry] OR "Berlin Questionnaire" OR "Clinical prediction tool*" OR "Clinical prediction rule*" OR "Clinical prediction score*" OR "Craniofacial structure*" OR "Epworth Sleepiness Scale" OR Mallampati OR "Multivariable Apnea Prediction Index" OR "Multivariable Apnoea Prediction Index" OR NAMES OR "Neck circumference" OR "Nocturnal choking" OR "Nocturnal gasping" OR oximetry OR oximetries OR "oxygen desaturation" OR photoplethysmography OR "Sleep Apnea Clinical Score" OR snoring OR "Snoring Scale" OR sleepiness OR "STOP-BAG" OR "STOP-Bang" OR "STOP Questionnaire" OR "Wisconsin Sleep Questionnaire"	14,409
#4	#1 AND #2	2,430
#5	#1 AND #3	2,541
#6	[mh "Diagnosis"] OR [mh "Diagnostic Tests, Routine"] OR [mh "False Negative Reactions"] OR [mh "False Positive Reactions"] OR [mh "Mass Screening"] OR [mh "Predictive Value of Tests"] OR [mh "ROC Curve"] OR [mh "Reproducibility of Results"] OR [mh "Sensitivity and Specificity"] OR accuracy OR diagno* OR "false negative" OR "false positive" OR "likelihood ratio" OR "predictive value" OR ROC OR reproducib* OR screen OR screening OR sensitivity OR specificity	593,628
#7	#4 AND #6	1,565
#8	#5 OR #7	3,137
#9	#8 NOT ([mh animals] NOT [mh humans])	3,137
#10	#9 NOT (Address:pt OR “autobiography”:pt OR “bibliography”:pt OR “biography”:pt OR “case control” OR "case report" OR “case reports” OR “case series” OR “comment”:pt OR "comment on" OR congress:pt OR “cross-sectional” OR “dictionary”:pt OR “directory”:pt OR “editorial”:pt OR “festschrift”:pt OR “historical article”:pt OR “interview”:pt OR lecture:pt OR "legal case":pt OR “legislation”:pt OR letter:pt OR “news”:pt OR “newspaper article”:pt OR “patient education handout”:pt OR “periodical index”:pt OR “retrospective cohort” OR ([mh "Animals"] NOT [mh "Humans"]) OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae)	2,979
#11	[mh Adult]	476,600
#12	#10 AND #11	1,064
#13	#12 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)	1,051
#14	#12 OR #13	1,064
#15	#14 with Cochrane Library publication date Between Jul 2020 and Dec 2021	32
#16	#15 AND ("randomized controlled trial":pt OR "randomized controlled trial as topic":pt OR "single-blind method":pt OR "double-blind method":pt OR "random allocation":pt)	32
#17	#16 with Publication Year from 2020 to 2021, in Trials	29

Embase, Interventions, 8-23-2021

Query	Results	No.
#1	'obstructive sleep apneas' OR 'obstructive sleep apnea'/exp OR 'obstructive sleep apnea' OR 'obstructive sleep apnea syndrome'/exp OR 'obstructive sleep apnea syndrome' OR 'obstructive sleep apnoeas' OR 'obstructive sleep apnoea'/exp OR 'obstructive sleep apnoea' OR osahs OR (('sleep apnea'/exp OR 'sleep apnea') AND ('hypopnea'/exp OR hypopnea)) OR 'sleep apnea syndromes'/exp OR 'sleep apnea syndromes' OR 'sleep disordered breathing'/exp OR 'sleep disordered breathing'	91,410
#2	'continuous positive airway pressure'/exp OR 'cpap device'/exp OR 'intermittent positive pressure ventilation'/exp OR 'mandible prosthesis'/exp OR 'positive end expiratory pressure'/exp/mj OR 'positive pressure ventilation'/exp OR bipap OR 'biphasic intermittent positive airway pressure' 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 'mandibular advancement device' OR 'mandibular advancement devices' OR 'oral appliance' OR 'oral appliances' OR pap:ti,ab	101,880
#3	#1 AND #2	22,401

Appendix B1. Original Search Strategies

Query	Results	No.
#4	#3 AND [humans]/lim	21,321
#5	#4 NOT ([editorial]/lim OR [letter]/lim OR [note]/lim)	19,095
#6	#5 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	9,881
#7	#5 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)	17,066
#8	#6 OR #7	17,594
#9	#8 AND [3-7-2020]/sd AND [2020-2021]/py	1,570
#10	'systematic review'/exp OR 'systematic review (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic literature review':ti,ab OR 'this systematic review':ti,ab OR 'umbrella review':ti,ab OR 'meta-analysis':ti,ab OR 'meta-analyses':ti,ab OR 'meta-synthesis':ti,ab OR 'meta-syntheses':ti,ab	525,233
#11	#9 AND #10	121
#12	#11 AND ([medline]/lim OR [pubmed-not-medline]/lim)	82
#13	#11 NOT #12	39
#14	'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)	8,715,214
#15	#9 AND #14	821
#16	#15 AND ([medline]/lim OR [pubmed-not-medline]/lim)	379
#17	#15 NOT #16	442
#18	#17 NOT #13	425

Embase, Screening, 8-23-2021

Query	Results	No.
#1	'sleep disordered breathing'/exp OR 'obstructive sleep apneas' OR 'obstructive sleep apnea' OR 'obstructive sleep apnea syndrome' OR 'obstructive sleep apnoeas' OR 'obstructive sleep apnoea' OR osahs OR ('sleep apnea' AND hypopnea) OR 'sleep apnea syndromes' OR 'sleep disordered breathing'	91,410
#2	'body mass'/exp OR 'body weight'/exp OR 'decision support system'/exp OR 'obesity'/exp OR 'psychometry'/exp OR 'snoring'/exp OR 'questionnaire'/exp OR instrument:ti,ab OR instruments:ti,ab OR questionnaire:ti,ab OR questionnaires:ti,ab OR scale:ti,ab OR scales:ti,ab	3,595,457
#3	'photoelectric plethysmography'/exp OR 'pulse oximetry'/exp OR 'berlin questionnaire' OR 'clinical prediction tool*' OR 'clinical prediction rule*' OR 'clinical prediction score*' OR 'craniofacial structure*' OR 'epworth sleepiness scale' OR mallampati OR 'multivariable apnea prediction index' OR 'multivariable apnoea prediction index' OR names OR 'neck circumference' OR 'nocturnal choking' OR 'nocturnal gasping' OR oximetry OR oximetries OR 'oxygen desaturation' OR photoplethysmography OR 'sleep apnea clinical score' OR snoring OR 'snoring scale' OR sleepiness OR 'stop-bag' OR 'stop-bang' OR 'stop questionnaire' OR 'wisconsin sleep questionnaire'	119,739
#4	#1 AND #2	45,189
#5	#1 AND #3	28,514
#6	'diagnosis'/exp OR 'diagnostic test'/exp OR 'false negative result'/exp OR 'false positive result'/exp OR 'mass screening'/exp OR 'predictive value'/exp OR 'receiver operating characteristic'/exp OR 'reproducibility'/exp OR 'sensitivity and specificity'/exp OR accuracy OR diagno* OR 'false negative' OR 'false positive' OR 'likelihood ratio' OR 'predictive value' OR roc OR reproducib* OR screen OR screening OR sensitivity OR specificity	12,622,950
#7	#4 AND #6	26,226
#8	#5 OR #7	41,450
#9	#8 AND [humans]/lim	39,286
#10	#9 NOT ([editorial]/lim OR [letter]/lim OR [note]/lim)	37,235
#11	#10 AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	21,467
#12	#10 NOT (child* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)	30,579
#13	#11 OR #12	32,261
#14	#13 AND [3-7-2020]/sd AND [2020-2021]/py	3,233
#15	#14 AND ([medline]/lim OR [pubmed-not-medline]/lim)	1,631
#16	#14 NOT #15	1,602

Appendix B1. Original Search Strategies

Query	Results	No.
#17	'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)	8,715,214
#18	#16 AND #17	1,054
#19	#18 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	286
#20	'cohort analysis'/exp OR 'epidemiological study' OR (cohort AND (study OR studies)) OR 'prospective study'/exp OR (prospective* AND cohort) OR 'cross-section*' OR 'cross section*' OR prognostic*:ti,ab OR prospectively:ti,ab	2,856,050
#21	#16 AND #20	596
#22	#21 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	224
#23	#22 NOT #19	90

Gray Literature

ClinicalTrials.gov, OSA in Adults, 8-23-2021

656 studies for Screening, 656 imported

Expert search:

("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 psychometrics OR instrument* OR questionnaire* OR scale* OR "oxygen desaturation" OR photoplethysmography OR diagno* OR sensitivity OR specificity OR accuracy OR reliab* OR valid* OR reproducib* OR "false positive" OR "false negative") AND AREA[ConditionSearch] "Apnea, Obstructive" AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] ("Adult" OR "Older Adult") AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[10/01/2015, 08/23/2021]

406 studies for Treatment and Harms combined search, 210 imported

Expert search:

AREA[StudyType] EXPAND[Term] COVER[FullMatch] “Interventional” AND AREA[ConditionSearch] EXPAND[Concept] “Apnea, Obstructive” AND AREA[InterventionSearch] (“Positive-Pressure Respiration” OR “Continuous Positive Airway Pressure” OR CPAP OR PAP 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”) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] (“Adult” OR “Older Adult”) AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[10/01/2015, 08/23/2021]

Appendix B2. Eligibility Criteria

Category	Include	Exclude
Populations	**KQs 1–3:** Adults age 18 years or older who are asymptomatic or have unrecognized symptoms of OSA **KQs 4–6:** Persons with a confirmed diagnosis of OSA; population may include asymptomatic or symptomatic adults **All KQs:** A priori subgroups of interest include those defined by age, sex, BMI category, and OSA severity*	**All KQs:** 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:** 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 1–3:** Populations screened for OSA in perioperative settings or screened in the context of occupational health examination to determine fitness for duty **KQs 4–6:** Interventions studied only in laboratories (e.g., studies of PAP conducted in sleep laboratories)
Screening	Externally validated questionnaires, including the ESS, STOP Questionnaire, Berlin Questionnaire, Wisconsin Sleep Questionnaire, or STOP-BANG Questionnaire; externally validated 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); combined screening approaches are also eligible, which may use a questionnaire or clinical prediction tool followed by home-based oximetry testing for persons who score above a defined threshold on the questionnaire or clinical prediction tool	Studies assessing single patient characteristics or risk factors
Treatment	Interventions appropriate for screen-detected or newly detected OSA, including PAP and MADs; variations of PAP are eligible, including continuous, auto-titrating, and bilevel with different device interfaces (e.g., nasal and oronasal masks) and accessory features such as humidification	All other interventions for OSA, including surgery, atrial overdrive pacing, medications, palatal implants, oropharyngeal exercises, tongue-retaining devices, positional alarms, nasal dilator strips, acupuncture, and auricular plaster; medications to treat sleepiness, sleep quality, or bruxism (rather than used to treat OSA), such as eszopiclone and modafinil; nasal steroids for treatment of allergic rhinitis or similar treatments that might secondarily improve OSA by treating another condition
Comparisons	**KQs 1, 3:** Screened vs. nonscreened groups or groups undergoing screening and/or diagnostic testing vs. groups not undergoing screening and/or diagnostic testing **KQ 2:** Studies on accuracy of screening must include a comparison with overnight PSG 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 **KQs 4–6:** PAP vs. control or sham PAP; MADs vs. no treatment or inactive MADs	**All KQs:** No comparison; nonconcordant historical controls; comparative studies of various interventions (e.g., comparing PAP with MADs or comparing different types of PAP) **KQ 2:** Studies with verification bias in which only a subgroup had PSG as the comparator

Appendix B2. Eligibility Criteria

Category	Include	Exclude
Outcomes	**KQs 1, 5:** 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), measures of sleepiness, motor vehicle crashes, cardiovascular events (including ischemic events and rhythm disturbances, such as incident atrial fibrillation), cerebrovascular events, incidence of heart failure, headaches, and cognitive impairment **KQ 2:** Sensitivity, specificity, discrimination, calibration **KQ 3:** False-positive results leading to unnecessary treatment, anxiety, condition-specific distress, or stigma **KQ 4:** Change in AHI, blood pressure **KQ 6:** Rash, irritation, need for additional sleep medications (e.g., to tolerate PAP), claustrophobia, oral or nasal dryness, epistaxis, pain, excess salivation, and tooth damage or loosening	All other outcomes **KQ 2:** Acceptability of screening
Study Designs	**KQs 1, 5–6:** RCTs **KQ 2:** Prospective cohort studies and cross-sectional studies that develop or evaluate screening questionnaires, clinical prediction tools, or combined screening approaches **KQ 3:** Studies eligible for **KQ 1** or **KQ 2** that report harms of screening or diagnostic tests **KQ 4:** Good-quality, recent (within last 5 years) systematic reviews reporting on change in AHI or blood pressure in studies comparing PAP or MAD with an eligible control	All other designs **KQ 2:** Questionnaires, tools, and tests not validated in a group of participants separate from the sample used to develop the test
Language	English	Languages other than English
Study Quality	Good or fair	Poor (according to design-specific USPSTF criteria)

* 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.

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; ESS=Epworth Sleepiness Scale; KQ=key question; MAD=mandibular advancement device; OSA=obstructive sleep apnea; PAP=positive airway pressure; PSG=polysomnography; RCT=randomized, controlled trial; RDI=Respiratory Disturbance Index; STOP=Snoring, Tiredness, Observed apnea, blood Pressure; STOP-BANG=Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference, and Gender; USPSTF=U.S. Preventive Services Task Force; vs.=versus.

Randomized, Controlled Trials and Cohort Studies

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 that are 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%); 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. In addition, intention-to-treat analysis is used for RCTs.

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. Intention-to-treat analysis is lacking for RCTs.

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. Intention-to-treat analysis is lacking for RCTs.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[281]

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of Ratings Based on Above Criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (greater than 100) of broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has a fatal flaw, such as uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[281]

Appendix C. Excluded Studies

X1: Non-English
X2: Ineligible Population
X3: Ineligible Screening
X4: Ineligible Treatment
X5: Ineligible Comparison
X6: Ineligible Outcome
X7: Ineligible Setting
X8: Ineligible Study Design
X9: Intermediate Outcome Only
X10: Ineligible Country
X11: Non-English Screener
X12: Abstract Only
X13: Poor Quality
X14: Irretrievable
X15: Irrelevant Systematic Review

1. Aarab G, Arcache P, Lavigne GJ, et al. The effects of mandibular advancement appliance therapy on jaw-closing muscle activity during sleep in patients with obstructive sleep apnea: a 3-6 months follow-up. *J Clin Sleep Med*. 2020 Sep 15;16(9):1545-53. doi: 10.5664/jcsm.8612. PMID: 32501212. Exclusion Code: X13.
2. Aarab G, Nikolopoulou M, Ahlberg J, et al. Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial on psychological distress. *Clin Oral Investig*. 2017 Sep;21(7):2371-8. doi: 10.1007/s00784-016-2045-3. PMID: 28083705. Exclusion Code: X6.
3. Abdeyrim A, Tang L, Muhamat A, et al. Receiver operating characteristics of impulse oscillometry parameters for predicting obstructive sleep apnea in preobese and obese snorers. *BMC Pulm Med*. 2016 Aug 22;16(1):125. doi: 10.1186/s12890-016-0284-3. PMID: 27549623. Exclusion Code: X3.
4. Abdeyrim A, Zhang Y, Li N, et al. Impact of obstructive sleep apnea on lung volumes and mechanical properties of the respiratory system in overweight and obese individuals. *BMC Pulm Med*. 2015 Jul 25;15:76. doi: 10.1186/s12890-015-0063-6. PMID: 26209328. Exclusion Code: X3.
5. Abdullah B, Idris AI, Mohammad ZW, et al. Validation of Bahasa Malaysia STOP-BANG questionnaire for identification of obstructive sleep apnea. *Sleep Breath*. 2018 Dec;22(4):1235-9. doi: 10.1007/s11325-018-1663-1. PMID: 29682698. Exclusion Code: X2.
6. Abumuamar AM, Dorian P, Newman D, et al. The STOP-BANG questionnaire shows an insufficient specificity for detecting obstructive sleep apnea in patients with atrial fibrillation. *J Sleep Res*. 2018 Dec;27(6):e12702. doi: 10.1111/jsr.12702. PMID: 29682848. Exclusion Code: X5.
7. Abuzaid AS, Al Ashry HS, Elbadawi A, et al. Meta-analysis of cardiovascular outcomes with continuous positive airway pressure therapy in patients with obstructive sleep apnea. *Am J Cardiol*. 2017 Aug 15;120(4):693-9. doi: 10.1016/j.amjcard.2017.05.042. PMID: 28651851. Exclusion Code: X8.
8. Adderley NJ, Subramanian A, Toulis K, et al. Obstructive sleep apnea, a risk factor for cardiovascular and microvascular disease in patients with type 2 diabetes: Findings from a population-based cohort study. *Diabetes Care*. 2020;43(8):1868-77. doi:

10.2337/dc19-2116. Exclusion Code: X8.

9. Ağan K, Özmerdivenli R, Değirmenci Y, et al. Evaluation of sleep in women with menopause: results of the Pittsburg Sleep Quality Index and polysomnography. *Journal of the Turkish German Gynecology Association*. 2015;16(3):149-52. doi: 10.5152/jtgga.2015.15087. Exclusion Code: X3.
10. Agarwal P, Ariga P, Jain AR. Efficacy of custom-made mandibular advancement appliance on patients with obstructive sleep apnea: A prospective clinical trial. *Drug Invention Today*. 2018;10(6):864-9. Exclusion Code: X5.
11. Agha M, Shehab-Eldin W, Helwa M. Obstructive sleep apnea in patients with type 2 diabetes mellitus. *Egyptian Journal of Chest Diseases and Tuberculosis*. 2019;68(4):560-6. doi: 10.4103/ejcdt.ejcdt_17_19. Exclusion Code: X5.
12. Ahlin S, Manco M, Panunzi S, et al. A new sensitive and accurate model to predict moderate to severe obstructive sleep apnea in patients with obesity. *Medicine (Baltimore)*. 2019 Aug;98(32):e16687. doi: 10.1097/md.0000000000016687. PMID: 31393370. Exclusion Code: X7.
13. Ahmad AN, McLeod G, Al Zahrani N, et al. Screening for high risk of sleep apnea in an ambulatory care setting in Saudi Arabia. *Int J Environ Res Public Health*. 2019 Feb 5;16(3)doi: 10.3390/ijerph16030459. PMID: 30764527. Exclusion Code: X3.
14. Aiyer A, Surani SR, Khan A. Influence of obesity on severity of sleep apnea and CPAP pressure requirement. *American Journal of Respiratory and Critical Care Medicine*. 2018;197(MeetingAbstracts). Exclusion Code: X6.
15. Aiyer I, Hesselbacher S, Surani Z, et al. Is epworth sleepiness score reliable as a screening tool for OSA? *Sleep Medicine*. 2019;64:S6. doi: 10.1016/j.sleep.2019.11.018. Exclusion Code: X8.
16. Aiyer I, Reddy S, Ramos Ramirez M, et al. Prevalence of normal Epworth sleepiness score in sleep apnea and gender influences. *Chest*. 2019;155(4):305A. doi: 10.1016/j.chest.2019.02.296. Exclusion Code: X6.
17. Akkurt BCO, Dogru S, Koyuncu O, et al. The relationship between disease severity and predictors of difficult intubation in patients with obstructive sleep apnea syndrome. 2015;31(1):67-71. Exclusion Code: X6.
18. Alessandri-Bonetti A, Bortolotti F, Moreno-Hay I, et al. Effects of mandibular advancement device for obstructive sleep apnea on temporomandibular disorders: A systematic review and meta-analysis. *Sleep Med Rev*. 2019 Dec;48:101211. doi: 10.1016/j.smrv.2019.101211. PMID: 31605905. Exclusion Code: X6.
19. Alessi CA, Martin JL, Fung CH, et al. Randomized controlled trial of an integrated behavioral treatment in veterans with obstructive sleep apnea and coexisting insomnia. *Sleep*. 2018;41:A155. Exclusion Code: X4.
20. Alhaddad A, Stansbury RC, Weaver B. Three-month adherence to positive airway pressure therapy for treatment of obstructive sleep apnea (OSA) in patients undergoing ambulatory versus in-lab pathways of care. results from a rural tertiary care academic center. *American Journal of Respiratory and Critical Care Medicine*. 2017;195doi: 10.1164/ajrccmconference.2017.C80F. Exclusion Code: X6.
21. Al-Jewair TS. High-quality randomized controlled trials are needed to confirm the effectiveness of oral appliances in the management of obstructive sleep apnea syndrome. *J Evid Based Dent Pract*. 2016 Jun;16(2):110-2. doi: 10.1016/j.jebdp.2016.05.002. PMID: 27449838. Exclusion Code: X8.
22. Allahwala UK, Cistulli P, Ciofani JL, et al. Influence of Obstructive Sleep

Appendix C. Excluded Studies

Apnoea on Outcomes in Patients With ST Elevation Myocardial Infarction (STEMI): the Role of the Coronary Collateral Circulation. *Heart Lung and Circulation*. 2021doi: 10.1016/j.hlc.2021.07.008. Exclusion Code: X5.

23. Allahwala UK, Cistulli PA, Dissanayake HU, et al. Influence of Obstructive Sleep Apnoea Severity on Coronary Collateral Recruitment During Coronary Occlusion. *Lung*. 2021doi: 10.1007/s00408-021-00462-6. Exclusion Code: X8.
24. Alonderis A, Raskauskiene N, Gelziniene V, et al. The association of sleep disordered breathing with left ventricular remodeling in CAD patients: a cross-sectional study. *BMC Cardiovasc Disord*. 2017 Sep 18;17(1):250. doi: 10.1186/s12872-017-0684-1. PMID: 28923022. Exclusion Code: X6.
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Appendix C. Excluded Studies

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129. Byun JI, Kim DH, Kim JS, et al. Usefulness of using alternative body-mass index and neck circumference criteria for STOP-bang questionnaire in screening South Korean obstructive sleep apnea patients. *Sleep Medicine Research*. 2020;11(1):38-43. doi: 10.17241/SMR.2020.00591. Exclusion Code: X2.
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interstitial lung disease: a quality of life analysis. *European Respiratory Journal*. 2016;48doi: 10.1183/13993003.congress-2016.PA2358. Exclusion Code: X8.

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function in patients with severe obstructive sleep apnea (CPAP-OASIS): A randomized, sham-controlled clinical trial. *Sleep Medicine*. 2017;40:e62. Exclusion Code: X9.

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179. Christensson E, Franklin KA, Sahlin C, et al. Can STOP-Bang and pulse oximetry detect and exclude obstructive sleep apnea? *Anesth Analg*. 2018 Sep;127(3):736-43. doi: 10.1213/ane.0000000000003607. PMID: 29958223. Exclusion Code: X2.
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186. Cistulli P. CPAP or oral appliances for OSA: Time for a personalised approach. *Journal of Sleep Research*. 2020;29(SUPPL 1)doi: 10.1111/jsr.13181. Exclusion Code: X8.
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193. Corral J, Sánchez-Quiroga M, Carmona-Bernal C, et al. Conventional polysomnography is not necessary for the management of most patients with suspected obstructive sleep apnea. Noninferiority, randomized controlled trial. *Am J Respir Crit Care Med*. 2017 Nov 1;196(9):1181-90. doi: 10.1164/rccm.201612-2497OC. PMID: 28636405. Exclusion Code: X3.
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for adaptive servoventilation (ASV): 2-year follow-up results. *Archives of Cardiovascular Diseases Supplements*. 2021;13(1):35. doi: 10.1016/j.acvdsp.2020.10.106. Exclusion Code: X2.

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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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

First Author, Year	Index Test	Reference Standard	Definition (AHI Cut Point) Used to Define OSA Based on Reference Standard	Bias Due to Patient Selection	Comments	Bias Due to Index Test	Comments	Bias Due to Reference Standard	Comments
Baird, 2018[282]	BQ	PSG: 95% in clinic; 5% in home	RDI >5	Unclear	Participants were part of a larger cross-sectional cohort study of Australian veterans. No description of how participants were selected for the larger study.	Unclear	Unclear whether the index and reference tests were interpreted separately; participants in the retrospective cohort (20% of participants) may have answered index questions differently based on their knowledge of their OSA diagnosis. Threshold for positive index test was not described clearly; however, authors reference separate study.	Unclear	A small proportion of patients (7%) had in-home PSG; unknown accuracy of in-home diagnosis.
Edmonds, 2019[115]	BQ	In-lab PSG	Separate accuracy for OSA severity: mild (AHI 5–14); mod (AHI 15–29); severe (AHI >30)	Low		Low	No description of whether the screening test was performed without knowledge of PSG, however this is unlikely to influence screening questionnaire responses. Thresholds were not prespecified in the methods; however, the results indicate that commonly used thresholds were used and likely were prespecified.	Low	None
Edmonds, 2019[115]	STOP-BANG	In-clinic PSG	Separate accuracy for OSA severity: Mild (AHI 5–14); mod (AHI 5–29); severe (AHI >30)	Low		Low	No description of whether the screening test was performed without knowledge of PSG, however this is unlikely to influence screening questionnaire responses. Thresholds were not prespecified in the methods; however, the results indicate that commonly used thresholds were used and likely were prespecified.	Low	None
Gurubhaga-vatula, 2013[114]	MVAP and MVAP+AHI from in-home PM	In-lab PSG	s-OSAS: AHI ≥30 and ESS >10 Any OSAS: AHI ≥5 and ESS >10	Low		Low	Eligible data for the OSA risk score is derived from a validation sample. Multiple cut points were evaluated to determine the optimal accuracy.	Low	None

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

First Author, Year	Index Test	Reference Standard	Definition (AHI Cut Point) Used to Define OSA Based on Reference Standard	Bias Due to Patient Selection	Comments	Bias Due to Index Test	Comments	Bias Due to Reference Standard	Comments
Hrubos-Strom, 2011[112]	BQ	In-lab PSG	AHI ≥5 and AHI ≥10	Unclear	A consecutive sample was used to recruit participants to complete the index test; the sample recruited for PSG oversampled the high-risk group, had higher ESS scores, and had higher rates of snoring.	Low		Low	None
Jorge, 2019[116]	BQ	In-lab PSG	Accuracy reported at multiple AHI cut points (dichotomized at >5, 15, and 30 events/hour)	Unclear	Some exclusion criteria apply to larger study on dementia in participants with and without OSA and may not be appropriate for purposes of screening for OSA (e.g., participants with other reasons for cognitive impairment, participants who slept <180 minutes during PSG).	Low	Unclear whether the index and reference tests were interpreted separately. However, because the index test is patient-reported, it is unlikely that participants' knowledge of their PSG results would affect scoring.	Low	None
Jorge, 2019[116]	Modified STOP-BANG	In-lab PSG	Accuracy reported at multiple AHI cut points (dichotomized at >5, 15, and 30 events/hour)	Unclear	Some exclusion criteria apply to larger study on dementia in participants with and without OSA and may not be appropriate for purposes of screening for OSA (e.g., participants with other reasons for cognitive impairment, participants who slept <180 minutes during PSG).	Unclear	Unclear whether the index and reference tests were interpreted separately. However, because the index test is patient-reported, it is unlikely that participant knowledge of their PSG results would affect scoring. Study used a cut point of >3 as high risk for severe OSA. Scoring does not appear to be prespecified, but this is unknown (developers of STOP-BANG suggest that >5 is high risk).	Low	None

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

First Author, Year	Index Test	Reference Standard	Definition (AHI Cut Point) Used to Define OSA Based on Reference Standard	Bias Due to Patient Selection	Comments	Bias Due to Index Test	Comments	Bias Due to Reference Standard	Comments
Morales, 2012[113]	MVAP score and MVAP plus AHI from in-home PM	In-lab PSG	Severe OSAS: AHI ≥30 and ESS >10	Unclear	Sample was recruited from a list of participants who were enrolled in a consumer membership program for older adults based on zip code. Multiple exclusion criteria included non-English speaking, MMSE score ≤20, use of sedatives/hypnotics, presence of alcoholism, inability to travel, and other conditions that could affect breathing. Recruitment also based on MVAP score (sought to recruit equal numbers of participants for each decile of MVAP score).	Low	Multiple cut points were evaluated to determine optimal accuracy.	Low	None
Shin, 2021[117]	Modified STOP-BANG	Portable PSG both in-lab and home testing (Embletta X100, unattended 11-channel)	Any OSA (AHI >5); subgroups of mild to moderate (5 < AHI < 30) and severe (AHI >30)	Unclear	Unclear sampling; participants from a large community-based cohort study. Authors noted that current sample included those who underwent a PSG but did not say how sample was selected for PSG.	Unclear	Index test results were taken from interviews and structured health exams based on cohort protocol; not stated whether results of PSG were known.	Low	Although a portable monitor was used with all patients (both in-home and in-clinic), the description of the monitor appears to include all the components of nonportable testing.

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

First Author, Year	Index Test	Reference Standard	Definition (AHI Cut Point) Used to Define OSA Based on Reference Standard	Bias Due to Patient Selection	Comments	Bias Due to Index Test	Comments	Bias Due to Reference Standard	Comments
Selvanathan, 2021[118]	Two-step screening: STOP-BANG + resting daytime Sp02, followed by Oxygen Desaturation Index values from overnight oximetry.	In-lab PSG	Any OSA (AHI >5); moderate to severe OSA (AHI >15); severe OSA (AHI >30)	Unclear	Although the study did not say whether a consecutive sample of patients was included, one of the papers from the study from which this was drawn used the same n of 204.	Low	Threshold was specified for STOP-BANG, daytime Sp02; threshold for overnight oximetry determined by assessing optimal AUC.	Low	None

Abbreviations: AHI=apnea-hypopnea index; BQ=Berlin Questionnaire; ESS=Epworth Sleepiness Scale; KQ=key question; lab=laboratory; MMSE=Mini-Mental Status Examination; mod=moderate; MVAP=Multivariable Apnea Prediction; OSA=obstructive sleep apnea; OSAS=obstructive sleep apnea syndrome; PM=portable monitor; PSG=polysomnography; RDI=respiratory disturbance index; OSAS=obstructive sleep apnea syndrome; STOP=Snoring, Tiredness, Observed apnea, blood Pressure.

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

First Author, Year	Bias Due to Flow and Timing	Comments	Overall Quality Rating	Comments	Are There Concerns That the Included Patients Do Not Match the Review Question?	Are There Concerns That the Index Test, Its Conduct, or Its Interpretation Differ From the Review Question?	Comments on Applicability
Baird, 2018[282]	High	Accuracy outcome is provided only for the overall sample (20% had prior PSG, 5% had home sleep test); no description of average timeframe between prior PSG and index test or proportion who were treated for OSA.	Poor	High risk of bias due to participant selection: 20% had prior PSG and may be aware of their diagnosis. No description of the proportion of participants with a prior PSG who were treated with OSA or the interval between the previous PSG and the screening questionnaire. Not all participants had the same reference standard; 5% had a home sleep test which may differ in diagnostic accuracy compared with in-lab PSG.	Yes	No	Sample includes Australian Vietnam veterans with and without PTSD who were recruited for a larger cohort study on the association between PTSD and sleep disturbance.
Edmonds, 2019[115]	Unclear	Study reports accuracy for mild, moderate, and severe OSA categories, but methods are unclear about how these were calculated. Based on data provided, estimates appear to reflect accuracy for "mild only" (vs. other severity or no OSA) and not "mild or worse" (same for moderate OSA estimates). When attempting to recreate estimates of accuracy, calculated values differ 1% to 4% from reported values.	Fair	Unclear whether screening and reference standard interpreted separately. Thresholds not clearly prespecified for screening tests; however, commonly used thresholds were used. Study reports accuracy for mild, moderate, and severe OSA categories, but methods are unclear about how these were calculated. When attempting to recreate estimates of accuracy, calculated values differ 1% to 4% from reported values.	Yes	No	Sample limited to participants with type 2 diabetes mellitus.

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

First Author, Year	Bias Due to Flow and Timing	Comments	Overall Quality Rating	Comments	Are There Concerns That the Included Patients Do Not Match the Review Question?	Are There Concerns That the Index Test, Its Conduct, or Its Interpretation Differ From the Review Question?	Comments on Applicability
Edmonds, 2019[115]	Unclear	Study reports accuracy for mild, moderate, and severe OSA categories, but methods are unclear about how these were calculated. Based on data provided, estimates appear to reflect accuracy for "mild only" (vs. other severity or no OSA) and not "mild or worse" (same for moderate OSA estimates). When attempting to recreate estimates of accuracy, calculated values differ 1%–4% from reported values.	Fair	Unclear whether screening and reference standard interpreted separately. Thresholds not clearly prespecified for screening tests; however, commonly used thresholds were used. Study reports accuracy for mild, moderate, and severe OSA categories, but methods are unclear about how these were calculated. When attempting to recreate estimates of accuracy, calculated values differ 1%–4% from reported values.	Yes	No	Sample limited to participants with type 2 diabetes mellitus.
Gurubhagavatula, 2013[114]	Unclear	All participants were invited for in-lab PSG, but 21% (52/250) did not follow through with testing. Missing data addressed using multiple imputation. Interval between index and reference test not clearly specified.	Fair	Some concern for bias arising from flow and timing; 21% of recruited sample did not have in-lab PSG; however, multiple imputation was used to address missing data.	Yes	No	Enrolled 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. Study limited to consecutive outpatients with HTN, recruited from a VA Medical Center and a university setting.
Hrubos-Strom, 2011[112]	Unclear	1,772 (of 9,319 eligible for random draws) were randomly drawn. Of those 1,772, 518 (29%) had PSG; the sample of 518 overrepresented the BQ high-risk group. Interval between index and reference test not clearly stated. Missing data on BQ were addressed by imputation.	Fair	Potential risk of bias due to participant selection and flow and timing. For comparison with PSG, study oversampled of high-risk participants (based on BQ score). Risk of bias due to flow and timing and missing data; however, would expect those biases to favor the accuracy of BQ—and this study did not find good accuracy.	Yes	No	Population-based sampling from Norway; clinical sample—the sample who had PSG oversampled the high-risk group, had higher ESS scores and rates of snoring.

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

First Author, Year	Bias Due to Flow and Timing	Comments	Overall Quality Rating	Comments	Are There Concerns That the Included Patients Do Not Match the Review Question?	Are There Concerns That the Index Test, Its Conduct, or Its Interpretation Differ From the Review Question?	Comments on Applicability
Jorge, 2019[116]	Unclear	Interval between index and reference test was not clearly specified; however, methods indicate they were both completed at enrollment in larger cohort study; 11% of participants excluded for analysis due to "invalid questionnaire."	Fair	Some exclusion criteria apply to larger study on dementia in people with and without OSA, and may not be appropriate for purposes of screening. Of the 91 assessed, 11 (12%) were excluded due to "invalid questionnaire."	Yes	No	Sample selected from outpatients attending a cognitive disorders clinic in Spain, recruited for a separate study on the cognitive progression of Alzheimer disease among those with and without OSA.
Jorge, 2019[116]	Low		Fair	Some exclusion criteria apply to larger study on dementia in those with and without OSA and may not be appropriate for purposes of screening for OSA. Study used a cut point of >3 as high risk for severe OSA. It does not appear to be prespecified, but this is unknown (developers of STOP-BANG suggest that >5 is high risk).	Yes	No	Sample was selected from outpatients attending a cognitive disorders clinic in Spain who were recruited for a separate study on the cognitive progression of Alzheimer disease among those with and without OSA.
Morales, 2012[113]	Unclear	All were invited for in-lab PSG, 19% (104/556) of all those screened did not receive PSG, primarily due to ineligibility (roughly 13% of those eligible declined). Of those enrolled, about 2% had incomplete data. Interval between index and reference standard not clearly stated.	Fair	Potential bias due to participant selection and flow and timing. All were invited for in-lab PSG, 19% (104/556) of all those screened did not receive PSG, primarily due to ineligibility (roughly 13% of those eligible declined). Of those enrolled, about 2% had incomplete data. Interval between index and reference standard not clearly stated.	Yes	No	All participants were age 65 years and older (mean age 71 years), had higher prevalence of sleepiness than would be expected (74% reported that they had a problem staying awake every day or several [≥3] days/week; 32% had ESS >10).

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

First Author, Year	Bias Due to Flow and Timing	Comments	Overall Quality Rating	Comments	Are There Concerns That the Included Patients Do Not Match the Review Question?	Are There Concerns That the Index Test, Its Conduct, or Its Interpretation Differ From the Review Question?	Comments on Applicability
Shin, 2021[117]	Unclear	Interval between reference and index test not described. Difference between those eligible/invited for PSG and sample included in analysis not clear. Note: Using data provided and the diagnostic accuracy calculator and Open Epi, neither the PPV nor the NPV for all OSA or mild to moderate was correct.	Fair	Unclear patient selection, index test, and flow and timing. Sample taken from larger cohort; authors stated the sample analyzed included those with PSG results (but no mention of whether all cohort participants were invited for PSG or a subsample). Index test—not stated whether results of PSG were known; unlikely but not able to say. Flow and timing—not stated whether results of PSG were known.	Yes	No	All patients were Korean adults.
Selvanathan, 2021[118]	Unclear	Only 2% (5/204) with PSG had missing data on screening test. No data on prevalence included so it is not possible to check accuracy.	Fair	Unclear ratings for patient selection (unclear whether patient selection was random or consecutive) and flow and timing (no data).	Yes	No	Participants were all patients on opioids for chronic pain; whether the results are applicable to a general population is not known.

Abbreviations: AHI=apnea-hypopnea index; BQ=Berlin Questionnaire; ESS=Epworth Sleepiness Scale; HTN=hypertension; KQ=key question; NPV=negative predictive value; OSA=obstructive sleep apnea; PPV=positive predictive value; PSG=polysomnography; PTSD=post-traumatic stress disorder; STOP=Snoring, Tiredness, Observed apnea, blood Pressure; VA=U.S. Department of Veterans Affairs; vs.=versus.

Appendix D Table 3. Relevance of Systematic Reviews and Meta-Analyses for KQ 4 (AHI and Blood Pressure Outcomes)

First author, Year	Did the review focus on studies of persons with a confirmed diagnosis of OSA randomized to an eligible treatment vs. control (PAP vs. control or sham PAP, and/or MADs vs. no treatment or inactive MAD) and report on change in AHI or blood pressure outcomes?	Did the review limit to RCTs or report pooled results separately for RCTs vs. other designs?	Did the review pool results for AHI and blood pressure outcomes?	Did the review limit to studies conducted in countries categorized as "Very High" on the UN Human Development Index (HDI) or report subgroup analyses by country setting?	Are there other factors related to the eligibility criteria of the review that differ from our own criteria for treatment studies?	What was the date of the last database search used to identify relevant studies?	Relevant?
Bartolucci, 2021[283]	Review included RCTs evaluating customized MADs vs. any comparator; of 50 included studies, approximately 12 compared MAD vs. inactive control.	Yes: However, results not pooled separately based on comparator.	Yes: However, not clear what proportion of pooled studies compared MAD with inactive control.	No limit on country setting was described; results did not comment on country setting.	Focus was on effectiveness of different customized MAD designs in reducing AHI vs. any control; no pooled subgroups based on comparators. Of the included studies, most compared MAD with another active therapy.	February 2020	No
de Vries, 2018[123]	Yes	Yes	Yes: 11	NR	No	December 31, 2016	Yes
Green, 2021[284]	Review included RCTs; methods are not clear about comparators.	Results for BP were pooled separately for RCTs.	Yes (10 RCTs comparing PAP vs. control pooled for BP outcomes).	No limit on country setting was described; results did not comment on country setting.	Yes: Main focus was on change in levels of catecholamines. Included RCTs reporting on BP had to also report on catecholamine levels.	May 2020	No
Ilea, 2019[285]	No: Included a variety of study designs, not just RCTs. Also did not clarify what the comparison is even from the RCTs. However, can identify which studies are RCTs.	Partially: Can use Table 1 for RCTs only, no meta-analysis for these.	No	NR	Yes: Variety of study designs and comparisons not clearly described.	2018	No
Labarca, 2021[124]	Yes	Yes	Yes: 6–8 studies included pooled BP outcomes (varies by BP measurement).	No limit on country setting was described; results did not comment on country setting.	Review was focused on studies that evaluated benefit of PAP vs. control for populations with resistant hypertension.	March 2020	Yes
Patil, 2019[125]	Yes	Yes	Yes: 11 for AHI, 26 for BP	NR	No	February 2018	Yes

Appendix D Table 3. Relevance of Systematic Reviews and Meta-Analyses for KQ 4 (AHI and Blood Pressure Outcomes)

First author, Year	Did the review focus on studies of persons with a confirmed diagnosis of OSA randomized to an eligible treatment vs. control (PAP vs. control or sham PAP, and/or MADs vs. no treatment or inactive MAD) and report on change in AHI or blood pressure outcomes?	Did the review limit to RCTs or report pooled results separately for RCTs vs. other designs?	Did the review pool results for AHI and blood pressure outcomes?	Did the review limit to studies conducted in countries categorized as "Very High" on the UN Human Development Index (HDI) or report subgroup analyses by country setting?	Are there other factors related to the eligibility criteria of the review that differ from our own criteria for treatment studies?	What was the date of the last database search used to identify relevant studies?	Relevant?
Rossi, 2021[286]	Review included RCTs comparing MAD vs. any comparator; approximately 8 (of 17 included studies) had an inactive comparator.	Review limited to RCTs but did not pool results of studies.	No	No limit on country setting is described; results do not comment on country setting.	Inclusion criteria state that RCTs enrolling fewer than 50 participants and those reporting on "secondary RCTs (studies with secondary analysis compared to the primary endpoint of the trial)" were excluded.	February 2019	No
Zhang, 2016[126]	Yes	Yes	Yes: 7	NR	No	April 1, 2016	Yes

Abbreviations: AHI=apnea-hypopnea index; BP=blood pressure; HDI=Human Development Index; KQ=key question; MAD=mandibular advancement device; NR=not reported; OSA=obstructive sleep apnea; PAP=positive airway pressure; RCT=randomized, controlled trial; UN=United Nations; vs.=versus.

Appendix D Table 4. Quality Ratings of Systematic Reviews and Meta-Analyses for KQ 4 (AHI and Blood Pressure Outcomes)

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?	Quality rating	Comments
de Vries, 2018[123]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	Includes good evidence of effect of oral appliances vs. inactive controls on two measures of BP. Seemed to have a good approach to assessing quality, bias, and heterogeneity.
Labarca, 2021[124]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	None
Patil, 2019[125]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	This study includes AHI and BP outcomes of interest but has many BP outcomes, see supplement figures S10-S33. Also assessed harms.
Zhang, 2016[126]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	Included pooled results for the effect of CPAP on AHI or ODI with 3 studies included, only 1 which presents AHI. Used Jadad scale to assess clinical trial quality.

Abbreviations: AHI=apnea-hypopnea index; BP=blood pressure; CPAP=continuous positive airway pressure; KQ=key question; MAD=mandibular advancement device; NA=Not applicable; NR=not reported; ODI=oxygen desaturation index; RCT=randomized, controlled trial.

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

First author, Year Trial name	Was random-ization adequate?	Was allocation conceal-ment adequate?	Were groups similar at baseline?	Was interven-tion 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[206] Nikolopoulou, 2020[207]	Yes	Yes	Yes	NA	MAD use 91% of nights nCPAP 83% of nights Intraoral pbo device 94% of nights	11%	13% (MAD: 5% vs. nCPAP: 18%), 5% (MAD: 5% vs. Intraoral pbo device: 10%) 8% (nCPAP: 18% vs. Intraoral pbo device: 10%)	Partially	No
Aarab, 2020[287]	Unclear	NR	Yes	NA	6.4 hours (1.8)*	28% overall 32% for ESS	4%	No	No
Andren, 2013[208]	Yes	NR	Mostly	Yes	NR	1%	3%	No	No
Arias, 2005[128]	NR	NR	Yes (cross-over study)	NA	7% were nonadherent (used <3.5 hours/night) and excluded from analysis; of the rest: CPAP: 6 hours/night; sham 6 hours/night	7%	7%	No	No
Baillieul, 2021[288]	Yes	Yes	No	NA	CPAP: 66% used device ≥4 hours/night Sham CPAP: 37% used device ≥4 hours/night	12.5%	25%	Yes	No
Ballester, 1999[160]	NR	NR	Yes	NA	Mean CPAP 5.2 hours/night; 73% used it >4.5 hours/night	0%	0%	No	No
Banghøj, 2021[161]	Yes	Unclear	Partially	NA	44% used CPAP >4 hours/night more than 70% of nights	17%	5.5%	No	No
Barbe, 2001[127]	Yes	NR	Yes	NA	CPAP: 5 hours/night; Sham: 4 hours/night	2%	2%	No	No
Barbe, 2010[162]	Yes	Yes	Mostly	NR	CPAP: mean use 4.7 hours/night	4%	6%	No	No
Barbe, 2012[163]	Yes	Yes	Yes, although AHI was a little higher in CPAP group	NA	CPAP: median 5 hours/night; 36% with mean use <4 hours/night	Loss to followup: 17%	1%	No	No

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

First author, Year Trial name	Was random-ization adequate?	Was allocation conceal-ment adequate?	Were groups similar at baseline?	Was interven-tion 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?
Barnes, 2004[164]	Yes	Yes	Yes	NA	CPAP: 3.6 hours/night; MAD: 5.5 hours/night; Pbo: 94.3%	23%	6%	Yes, high overall	No
Bigini, 2019[289]	Yes	Yes†	NR	NR	Calculated mean CPAP: 5.3 hours/night	23%	43%	Yes	No
Bloch, 2000[209]	Yes	NR	Yes (cross-over study)	NA	MADs: ≥4–7 nights/week No treatment: NA	0%	NA	No	No
Campos-Rodriguez, 2006[129]	NR	Unclear	Yes	NA	5.0 vs. 4.4 hours/day for CPAP vs. sham	6%	0%	No	No
Campos-Rodriguez, 2016[165]	Yes	Yes	Minor‡ differences between CPAP vs. control in mean age (56 vs. 59), % smokers (47 vs. 36), and % using sedative drugs (23 vs. 28)	NA	5% did not tolerate or begin CPAP; mean use was 4.8 hours/day (SD: 2.5) in those who began CPAP	3%	0%	No	No
Caples, 2019[290]	Yes	Yes	Yes	NA	Mean 6 hours, 60% <4 (3 months) and 71.8% >4 (12 months)	42%	9%	No	2 crossed over
Chasens, 2014[130]	Yes	NR	Partially	NA	74% adherent for ≥4 hours/night	4.3%	9%	No	No
Chong, 2006[131]	NR	No	Yes	NA	5.2 hours/night	5%	0%	No	No
Coughlin, 2007[132]	Yes	NR	Yes (cross-over)	NA	CPAP: 3.9 hours/night; Sham CPAP: 2.6 hours/night	3%	0%	No	No
Craig, 2012[166] MOSAIC	Yes	Yes	Yes	NA	Median CPAP usage: 2.39 hours/night (IQR: 0.36 to 4.59)	13% for the coprimary outcome ESS (lower for some secondary outcomes)	For ESS: 0% CPAP: 25 (13%) Standard: 25 (13%)	No	No

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

First author, Year Trial name	Was random-ization adequate?	Was allocation conceal-ment adequate?	Were groups similar at baseline?	Was interven-tion 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?
Dalmases, 2015[167]	Yes	Yes	Yes	NA	NR	6%	0%	No	No
Durán-Cantolla, 2010[133]	Yes	Yes	Yes	NA	Mean 4.2 (sham) to 4.5 (CPAP) hours/day over 12 weeks; 59% (sham) and 65% (CPAP) used >4 hours/day	20% did not complete the trial (either refused to continue, were intolerant of CPAP, had protocol violation, or had technical problems)	2%	Borderline for overall attrition; no for differential attrition	No
Durán-Cantolla, 2015[210]	Yes	Yes	NA (cross-over)	NA	MAD: 6.4 hours/night; Pbo: 6.2 hours/night	10%	5%	No	No
Egea, 2008[134]	NR	NR	Yes based on N randomized, but partially based on N analyzed	NA	NR	18%	4%	No	No
Engleman, 1994[168]	NR	NR	Yes	NA	CPAP: mean 3.7 hours/night	9%	Unclear	No	No
Engleman, 1997[169]	NR	NR	Yes	NA	CPAP mean 3.2 hours/night	11%	20%	Partially	No
Engleman, 1998[170]	NR	NR	Yes	NA	Mean CPAP runtime: 3.2 hours/night; effectively used 2.8 hours/night	0%	0%	No	No
Engleman, 1999[171]	NR	NR	Yes	NA	CPAP 3.5 hours/night	8%	NR (at most 8%)	No	No
Faccenda, 2001[172]	NR	NR	Yes (cross-over study)	NA	47% of patients used CPAP ≥3.5 hours/night; mean use 3.3 hours/night; pbo adherence almost 100%	4%	2%	No	No
Gagnadoux, 2017[216]	Yes	Yes	No, but only a few differences	NA	6.6 hours/night in effective MAD group; 96.1% compliance	18%	1%	No	No

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

First author, Year Trial name	Was random-ization adequate?	Was allocation conceal-ment adequate?	Were groups similar at baseline?	Was interven-tion 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?
Gottlieb, 2014[173] Lewis, 2017[174] HeartBEAT	Yes	Yes	Partially	NA	CPAP: 3.5 hours/night Mean oxygen: 4.8 hours/night	12% for primary outcome; 5% to 7% for other outcomes	3% to 7%	No	No
Haensel, 2007[135]	NR	NR	Yes	NA	CPAP: 6.6 hours/night; Sham CPAP: 6.0 hours/night	0%	0%	No	No
Hoyos, 2012[136]	Yes	Yes	Yes	NA	CPAP: 3.6 hours/night; Sham CPAP: 2.8 hours/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[137]	NR	NR	Yes	NA	CPAP: 5.1 hours/night; Sham: 2.6 hours/night	18%	0%	No	No
Jackson, 2021[175] Jackson, 2019[176]	Unclear	Unclear	No	NA	CPAP group used their CPAP for an average of 4.5 (2.6) hours/night	15%	10.6%	No	No (Note: pool together CPAP and CPAP plus education groups)
Jenkinson, 1999[138] Hack, 2000[139]	NR	Yes	Yes	NA	CPAP: 5.4 hours/night; Sham: 4.6 hours/night	6%	4%	No	No
Johnston, 2002[214]	NR	NR	Yes	NA	MAD 68% every or almost every night; 79% ≥4 hours/night	5%	5%	No	No
Jones, 2013[140]	Yes	NR	Yes	NA	CPAP: 3.0 hours/night; Sham CPAP: 2.0 hours/night	19%	5%	No	No
Kushida, 2012[141] Batool-Anwar, 2016[142] APPLES	Yes	Yes	Yes	NA	CPAP: 5.8 hours/night; Sham: 4.3 hours/night	23% (for ESS at 6 months; varies by outcome and timing)	5%	Yes	No
Lam, 2007[177]	Yes	NR	Yes	NA	CPAP: 4.2 hours/night; MAD: 6.4 hours/night	10%	3% to 12%	Partially	Partially
Lam, 2010[143]	Yes	NR	Yes	NA	CPAP: 6.2 hours/night; Sham: 4.5 hours/night	0%	0%	No	No

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

First author, Year Trial name	Was random-ization adequate?	Was allocation conceal-ment adequate?	Were groups similar at baseline?	Was interven-tion 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?
Lee, 2011[144]	NR	NR	Yes	NA	CPAP: 5.0 hours/night; Pbo CPAP: 6.9 hours/night	NR, presume 0	NR, presume 0	No	No
Lim, 2007[178]	NR	NR	Yes	NA	NR	0	0	No	No
Loredo, 2006[145]	NR	NR	Yes	NA	CPAP: 6.6 hours/night; Sham CPAP: 6.0 hours/night	Unclear which exclusions were prior to vs. after randomization (maximum would be 17%)	NR	No for overall; unclear for differential	No
Lui, 2020[179]	Yes	NR	Yes	NA	55.6% (treatment group) >4 hours/night	No attrition, though noncompliance used in per-protocol analysis	0%	No	No
Malow, 2008[219]	Yes	Yes	Yes	NA	CPAP: 4.7 hours/night; Sham CPAP: 3.6 hours/night	9%	14%	Yes; all noncompleters were from G1; 9% of G1 dc due to inability to tolerate CPAP, perhaps due to higher severity	No
Marklund, 2015[217]	Yes	Yes	Partially	NA	Active appliance group wore for mean of 86% of nights, pbo for 83% of nights, >75% of those in both groups wore for full night	5%	2%	No	No
Marshall, 2005[146]	Yes	Yes	Yes (cross-over study)	NA	CPAP: 4.9 hours/night; Sham CPAP 4.9 hours/night	7%	<1%	No	No
Martinez-Garcia, 2013[180] HIPARCO	Yes	Yes	Yes	NA	CPAP: 5 hours/night; 72% ≥4 hours/night	10%	2%: CPAP: 11/98=11%; Control: 9/96=9%	No	No

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

First author, Year Trial name	Was random-ization adequate?	Was allocation conceal-ment adequate?	Were groups similar at baseline?	Was interven-tion 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?
Martínez-García, 2015[181]	Yes	Yes	Yes	NA	69.9% >4 hours	17.9%	27.4%	Yes	No
Masa, 2015[182] Pickwick	Yes	Yes	Partially, no formal statistical comparison, appear to be some slight differences in various comorbidities and drinking	NA	Mean compliance 5.3 hours/day	CPAP and control only: 9.3% (14/150) CPAP, NIV, and control: 9.5% (21/221)	10%	No	No
McArdle, 2001[183]	Yes	Yes	NA (cross-over)	NA	Median 4.5 hours/night	4%	4%	No	No
McMillan, 2014[184] PREDICT	Yes	Yes	Partially	Yes	71% reported still using CPAP at 12 months; at 3 months, median usage of 1 hour 52 minutes per night; at 12 months, 2 hours 22 minutes/night 35% at 3 months and 35% at 12 months used CPAP >4 hours/night	17%	4%: CPAP: 26/140=19% BSC: 21/138=15%	No	No
Melehan, 2018[147]	Yes	Yes	Yes	NA	≥4 hours/night: 39% of CPAP users (mean use 3.7 hours/night) and 27% of sham users (2.6 hours/night)	10%	7%	No	No
Montserrat, 2001[148]	Yes	NR	Partially	NA	CPAP 4.3 hours/night; sham 4.5 hours/night	4%	0%	No	No
Naismith, 2005[211] Gotsopoulos, 2002[212] Gotsopoulos, 2004[213]	Yes	Yes	Yes (cross-over study)	NA	Both MAD and sham MAS: 6.7 hours/night; 96% to 97% of nights	9%	5%	No	No
Neikrug, 2014[149]	Yes	NR	Yes	NA	CPAP: 5.2 hours/night	18%	5%	No	No

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

First author, Year Trial name	Was random-ization adequate?	Was allocation conceal-ment adequate?	Were groups similar at baseline?	Was interven-tion 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?
Ng, 2018[197]	Yes	Unclear	Yes	NA	71% used CPAP >4 hours/night (mean 5 and 5.2 hours/night at 1 and 3 months, respectively)	19%	13%	Yes	No
Nguyen, 2010[150]	NR	NR	Yes	Yes	Assessed but NR	0%	0%	No	No
Peker, 2016[185] Balcan, 2019[186] Celik, 2021[187] Celik, 2021[198] Wallstrom, 2019[200] RICCADSA	Unclear	Yes	Yes	NA	4.4–6.6 hours/night (1 month to 6 years)	41% based on primary outcome, unclear on depression and anxiety outcomes	12% based on primary outcome, unclear on depression and anxiety outcomes§	Yes	Partially (22 of the no CPAP group started CPAP during the full study, 5 within the first year, which is the period for the Celik and Balcan studies), would bias the results toward the null
Pepperell, 2002[151] Kohler, 2008[152]	NR	NR	Yes	NA	CPAP: 4.9 hours/night; Sham CPAP: 4.5 hours/night	20% (for missing blood pressure data)	1% (for blood pressure outcomes)	No	No
Petri, 2008[218]	Yes	Yes	Yes	NA	NR	13%	1%-15%	Partially (G1 vs. G3)	No
Phillips, 2011[153]	Yes	Yes	Yes	NA	CPAP: 4.4 hours/night; Sham CPAP: 3.4 hours/night	24%	5%	Yes overall, but not differential	No
Ponce, 2019[188]	Yes	Yes	Yes	NA	73% ≥4 hours/night	ESS: 2.1% QSQ: 4.8%	NR	No	No
Quinnell, 2014[215] TOMADO	Yes	Yes	Yes	NA	Mean (SD) for 3 MAD groups: 4.4 (2.4) to 5.7 (2.0) hours/night	18% did not complete; 8% not analyzed	Low when comparing most groups, but high for bMAD group vs. others (17% to 30% differential)	Yes (high differential attrition for bMAD group compared with other groups)	No

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

First author, Year Trial name	Was random-ization adequate?	Was allocation conceal-ment adequate?	Were groups similar at baseline?	Was interven-tion 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?
Redline, 1998[189]	Yes	NR	Mostly (slightly higher RDI in CPAP arm, and fewer women)	NA	CPAP: 44% of sleep time; 3.1 hours/night CT: 82% of nights	13%	2%	No	Possibly[ll]
Robinson, 2006[154]	NR	Yes	Yes	NA	CPAP: 5.2 hours/night; Sham CPAP: 4.3 hours/night	9%	9%	No	No
Ruttanaum-pawan, 2008[190] Kaneko, 2003[191]	NR	NR	Partially; higher AHI in control, but they adjusted for it in analyses	NA	CPAP: 6.2 hours/night	NR, presume 0	NR, presume 0	No	No
Salord, 2016[192]	Yes	Yes	Yes	NA	Mean 5.4 hours per night, 86% >4 hours at 12 weeks	Tx: 9 lost, 3 noncomplete (22%) C: 6 lost (13%)	9%	No	NR
Schwarz, 2018[291]	Yes	NR (reported blinding for patients and outcome assessors, but NR for others on the research team such as those enrolling participants)	Yes, except the therapeutic group had more patients with HTN	NA	6 to 7 hours per night	46.6%	9% (12/23 [52%] vs. 9/22 [41%])	Yes	No
Shaw, 2016[193]	Yes	Yes	Yes	NA	Mean PAP use: 3 hours/night at 3 months; 4.9 hours/night at 6 months 45% adherent at 3 months; 61.3% adherent at 6 months	14.1%	13.8%	Yes; there was 14% differential attrition due to treatment intolerance in the intervention arm	No

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

First author, Year Trial name	Was random-ization adequate?	Was allocation conceal-ment adequate?	Were groups similar at baseline?	Was interven-tion 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?
Siccoli, 2008[155]	NR	NR	Yes	NA	CPAP: 4.7 hours/night; Sham CPAP: 3.9 hours/night	3%	2%	No	Possibly: 52 has been involved in previous study on CPAP effect on BP
Smith, 2007[156]	Yes	NR	Yes	NA	CPAP: 3.5 hours/night; Sham: 3.3 hours/night	15%	Unable to determine	No	No
Tomfohr, 2011[194]	NR	NR	Yes	NA	CPAP: 5.5 hours/night; Sham CPAP: 6.6 hours/night	17%	4%	No	No
Traaen, 2021[199]	Yes	Yes	Unclear	NA	66.7% used CPAP ≥4 hours/night (mean 5.3 hours/night)	5%	2%	No	No
Weaver, 2012[157] CATNAP	Yes	Yes	Yes, except slightly higher score on mental health component of SF-36 for sham CPAP group	NA	CPAP: 4.0 hours/night; Sham: 3.1 hours/night	Overall: 21% who were randomized were not included in analyses (15% withdrew prior to receiving CPAP or sham; another 6% were missing for the primary outcome)	1%	Yes, high overall	No
Weinstock, 2012[201] Redline, 2014[220]	Yes	NR	Yes	NA	Mean CPAP use: 4.8 hours/night Mean sham CPAP: 3.4 hours/night; p<0.1	2% (1 participant completed the first [CPAP] period only)	4%	No	No
West, 2007[158] West, 2009[159]	Yes	NR	Yes	NA	CPAP: 3.6 hours/night; Sham CPAP: 3.3 hours/night	5%	0%	No	No
Wimms, 2020[195] MERGE	Yes	Yes	Yes	NA	Median CPAP use: 4 hours/night (range, 1.36–5.44)	10%	5%	No	No

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

First author, Year Trial name	Was random-ization adequate?	Was allocation conceal-ment adequate?	Were groups similar at baseline?	Was interven-tion 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?
Zhao, 2017[196] BestAIR	Yes	Yes	Yes	NA	Mean CPAP use, first 6 months: 3.8 hours/night; 51.8% used for ≥4 hours/night (43.4% adherent by Medicare definition; Note: adherence data only available for one arm [CPAP] out of 4 arms)	18%	0.5%	No	No

* We used the data from Table 4 and not the text of the publication. There was a discrepancy between the two.
† Answered using the study's methods article: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6311443/.
ǂ The BMI difference was statistically significant, but mean difference was very small and unlikely clinically important (33.8 vs. 33.5).
§ Depression and anxiety participants were only included if they had data available.
ǁ Subjects with symptoms of nasal congestion were provided with a nasal steroid spray, and it is NR whether there was an equal proportion of such patients in each arm. Control patients got nasal dilator strips.

Abbreviations: AHI=apnea-hypopnea index; APPLES=Apnea Positive Pressure Long-term Efficacy Study; BSC=best supportive care; BestAIR=Best Apnea Interventions for Research; bMAD=fully bespoke mandibular advancement device; BMI=body mass index; BP=blood pressure; BQ=Berlin Questionnaire; CATNAP=CPAP Apnea Trial North American Program; CPAP=continuous positive airway pressure; CT=conservative therapy; ESS=Epworth Sleepiness Scale; G=group; HeartBEAT=Heart Biomarker Evaluation in Apnea Treatment; HTN=hypertension; IQR=interquartile ratio; KQ=key question; MAD=mandibular advancement device; MAS=mandibular advancement splint; MOSAIC=Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular; MVAP=Multivariable Apnea Prediction; N=number; NA=not applicable; nCPAP=nasal continuous positive airway pressure; NIV=noninvasive ventilation; NR=not reported; OSA=obstructive sleep apnea; PAP=positive airway pressure; pbo=placebo; PSG=polysomnography; QSQ=Quebec Sleep Questionnaire; RCT=randomized, controlled trial; RDI=respiratory disturbance index; SD=standard deviation; SF-36=Medical Outcome Short-Form (36-Item) Health Survey; STOP=Snoring, Tiredness, Observed apnea, blood Pressure; TOMADO=Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea-hypopnoea; tx=treatment; vs.=versus.

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

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[206] Nikolopoulou, 2020[207]	Yes	Partially	NR	Partially; both oral appliance groups were masked for question-naires	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 pbo. Only the comparison of the active and sham oral device was masked; patients receiving CPAP were not masked.
Aarab, 2020[287]	Yes	No	No	No	Yes	None	No	Poor	High attrition, inappropriate statistical methods, no adjustment for potential confounders, unlikely that analysis of ESS considered baseline values to guard against risk of bias.
Andren, 2013[208]	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 nonadherent patients from analysis, but N=2. No description of randomization or blinding of assessors.

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

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
Baillieul, 2021[288]	Yes	Yes	Yes	Yes	Yes - ESS Unclear-MMSE	None	No	Poor	Baseline AHI was higher in the CPAP group than Sham CPAP (54 vs. 38 events/hour); other measures of OSA severity were also higher in CPAP group (e.g., ODI, time spent with Sp% <90%). Adherence was lower in the Sham CPAP vs. CPAP group (37% vs. 66%), suggesting participants may have been aware of treatment assignment. Small sample size (n=24) with differential attrition of 25% due to 3 participants lost to followup in the CPAP arm. No analysis to address missing data.
Ballester, 1999[160]	Yes	No	No	No	Yes	NR, but suggests there was no missing data	Yes	Fair	No masking; methods of randomization and allocation concealment NR.
Banghøj, 2021[161]	Yes	No	No	No	Yes	NR	NR, did not use ITT but used controlled regressions	Fair	Differences based on BMI, no information on concealment, adherence to CPAP was low. Masking not possible. No information on how missing data were handled, mention some missing data for some outcomes, not sure if it affected ESS. Looks like they only included those with completed CGM data but probably did not affect ESS data.
Barbe, 2001[127]	Yes	Yes	NR	Yes	Yes	Excluded	Yes	Fair	Methods of allocation concealment NR.

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

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
Barbe, 2010[162]	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 are low and unlikely to bias results.
Barbe, 2012[163]	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 24-hour 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).
Barnes, 2004[164]	Yes	Yes	NR	NR	Yes	Multiple imputation	Yes	Fair	Risk of attrition bias; masking of providers and outcome assessors NR.
Bigini, 2019[289]	Yes: Pittsburgh Sleep Quality Index; ESS	Yes	Yes*	No: PSIQ and ESS are self-report	Yes	None	No	Poor	Very small subset of patients enrolled in a large, randomized trial that has not yet been reported. It is unclear whether the subsample was randomly selected. Significant attrition and attrition differences.
Bloch, 2000[209]	Yes	No	NR	NR	Yes	NA	Yes	Fair	Open-label trial for patients; other masking NR; sequential open-label tx could bias self-reported outcomes.

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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
Campos-Rodriguez, 2006[129]	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 whether the person assigning to treatment groups was the person who knew the sequence and filled the envelopes).
Campos-Rodriguez, 2016[165]	Yes	No	Partially	Partially	Yes	Imputed (baseline observation carried forward) for QSQ; unclear for other measures	Yes	Fair	Some baseline differences between groups (control group slightly older and higher proportion were using sedative drugs). Those in treatment arm had additional visits for mask fitting; however, authors stated that no additional counseling was provided. Missing data were addressed for primary outcome only; however, overall attrition was low and not differential.
Caples, 2019[290]	Yes	No	NR	NR	Yes	NR	NR	Poor	Small study, 42% lost to followup, low external validity.
Chasens, 2014[130]	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.
Chong, 2006[131]	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).

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

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
Coughlin, 2007[132]	Yes	Yes	Yes	Yes	Yes	Excluded	Yes	Good	Only 1 person lost/excluded, and since it is cross-over, not a big concern.
Craig, 2012[166] MOSAIC	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).
Dalmases, 2015[167]	Yes	No	No	Partially (some patient reported and not blinded)	Yes	NR	NR	Fair	Did not use ITT, unclear how missing data were handled. Providers and pts unable to be masked.
Durán-Cantolla, 2010[133]	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[210]	Yes	Yes	Yes	Yes	Yes	NR; looks like excluded	Partially	Good	Small amount of missing data excluded.
Egea, 2008[134]	Yes	Yes	NR	Partially	Yes	Excluded	Partially	Fair	Completer's analysis, no information on randomization, blinding of outcome assessors other than pts.

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

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, 1994[168]	Yes	Yes	NR	NR	Yes	Excluded from analysis	Yes, other than exclusion of missing	Fair	Self-reported outcome assessors masked because patients were masked.
Engleman, 1997[169]	Yes	Yes	NR	NR	Yes	Excluded from analysis	Yes, other than exclusion of missing	Fair for cognitive out-comes; Poor for ESS	Only 9 of 18 reported ESS, unclear how many from each arm.
Engleman, 1998[170]	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.
Engleman, 1999[171]	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[172]	Yes	Yes	NR	Yes	Yes	Excluded	Yes	Fair	Consider patients masked because they were told that pbo 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-hour BP monitor, consider outcome assessors masked.
Gagnadoux, 2017[216]	Yes	Yes	No	Yes	Yes	Multiple imputation for primary measures, but no information regarding secondary measures (i.e., ESS, OSA symptoms)	Yes	Fair	Some baseline differences that may have introduced bias: significantly more women in the MAD arm, and more than twice as many current smokers in the sham arm as the MAD arm (difference nearly significant).

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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
Gottlieb, 2014[173] Lewis, 2017[174] 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[135]	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[136]	Unclear	Yes	Yes	Yes	Yes	None	No, completers analysis	Fair	Moderate risk of attrition bias, but it was nondifferential for outcomes eligible for our review (ESS, BP); no handling of missing data; completers analysis.
Hui, 2006[137]	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.
Jackson, 2021[175] Jackson, 2019[176]	Yes	No	No	Partially	Yes	Multiple imputation	Yes	Fair	No details provided on randomization and concealment process. Patients and providers unable to be masked. Outcome assessors partially masked, clinical interviews were blinded but ESS was not. Somewhat high differential attrition (10.6 percentage points).
Jenkinson, 1999[138] Hack, 2000[139]	Yes	Yes	No	Yes	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
Johnston, 2002[214]	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[140]	Yes	Yes	Yes	Yes	Yes	Excluded non-completers	Yes	Fair	Inadequate methods of handling missing data, allocation concealment NR.
Kushida, 2012[141] Batool-Anwar, 2016[142] APPLES	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[177]	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 as much concern about MAD vs. control; similar rates of attrition.
Lam, 2010[143]	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).
Lee, 2011[144]	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 weeks is long enough for cognitive changes.

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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
Lim, 2007[178]	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 noted that 2 weeks may not be sufficient time to assess for improvements in some neurocognitive measures.
Loredo, 2006[145]	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; 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.
Lui, 2020[179]	Yes	No	No	No	Yes	NA	Yes	Fair	CPAP vs. no treatment control, not masked, low adherence at 56% to CPAP >4 hours/night.
Malow, 2008[219]	Yes	Yes	Yes	Yes	Yes	Excluded	Partially	Fair	Only usable outcome in this study is AHI, and it is only at 2 nights; pilot/feasibility study not designed to examine efficacy.
Marklund, 2015[217]	Yes	Yes	No	Yes	Yes	NR	No, however did used controlled regressions for analyses if continuous outcomes	Fair	Not ITT (although relatively few dropped out), differences in age at baseline, no information on missing data, providers unable to be masked.
Marshall, 2005[146]	Yes	Yes	Yes	Yes	Yes	Excluded	Partially	Good	Excluded nonadherent patients from analysis, but N=2. Adjusted appropriately.
Martinez-Garcia, 2013[180] HIPARCO	Yes	No	No	No	Yes	Multiple imputation	Yes	Fair	ESS is patient rated and thus could be biased.

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

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
Martínez-García, 2015[181]	Yes	No	No	Yes	Yes	Imputed	ITT	Fair	High overall attrition (18%) and differential attrition (27%, higher in control group); imputation used to address missing data in analysis. However, unclear whether those lost to followup had worse outcomes at baseline or higher rates of OSA symptoms during study. Potential for reporting bias; sleep-related QOL measure reported as individual domain scores only, not overall score.
Masa, 2015[182] Pickwick	Yes	No	No	No	Yes	Multiple imputation	Yes	Fair	May be some differences at baseline in comorbidities, differential attrition close to 10%, and unclear if providers and assessors were blinded (probably not a major concern). Also note that noninvasive ventilation is one of the tx arms.
McArdle, 2001[183]	Yes	Yes	NR	Yes	Yes	NR	Mostly	Fair	Very small sample size; missing data excluded.
McMillan, 2014[184] PREDICT	Yes	No	No	No	Yes	Sensitivity analyses with multiple imputation	Yes	Fair	Eligible outcomes were questionnaires filled out by patients who were not blinded.
Melehan, 2018[147]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes: ITT	Fair	Not clear whether sexual function is acceptable outcome. Secondary outcomes do not have means associated with them, only a statement that there were no CPAP related differences. Adherence generally low.
Montserrat, 2001[148]	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.

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

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
Naismith, 2005[211] Gotsopoulos, 2002[212] Gotsopoulos, 2004[213]	Yes	Yes	Yes	Yes	Yes	Conducted both ITT and completers	Yes	Good	
Neikrug, 2014[149]	Yes	Yes	No	Yes	Yes	None, excluded	Other than no handling of missing data, acceptable methods	Fair	
Ng, 2018[197]	Yes	No	No	Partially	Yes	ITT	Yes	Fair	Potential for selection bias was present because a portable home study, rather than PSG, was used to diagnose OSA, possibly leading to some missed cases. Overall attrition and differential attrition of 19% and 13%, respectively, may have introduced potential bias, but there is no evidence this substantially affected findings. Several important factors—baseline asthma control, sleepiness, and nocturnal symptoms—were similar between those who dropped out and study completers. Unclear if allocation concealment was used in randomizing the sample. This paper did not report whether allocation concealment took place in the article or supplement. There was no sham CPAP, so the study is not blinded. Outcomes are non-OSA related questionnaires, but it was not stated whether questionnaires were administered by someone blinded. This study had appropriate adherence. The attrition is higher in control arm.

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

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
Nguyen, 2010[150]	Yes	Yes	NR	Yes	Yes	NA	NR	Fair	Multiple ROB domains NR (e.g., randomization, allocation concealment, and adherence).
Peker, 2016[185] Balcan, 2019[186] Celik, 2021[187] Celik, 2021[198] Wallstrom, 2019[200] RICCADSA	Yes	No	No	Partially	Yes	LOCF, imputation	Yes	Fair	Group assignment was based on the cardiorespiratory PG recordings, unable to mask patients and providers. High attrition for the Peker study, but very long followup, appears to be differential attrition in Celik and Balcan, but some lack of clarity on attrition and sample sizes.
Pepperell, 2002[151] Kohler, 2008[152]	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).
Petri, 2008[218]	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 those results are not presented.
Phillips, 2011[153]	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.
Ponce, 2019[188]	Yes	No	No	Not for ESS or QSQ	Yes	ITT with multiple imputation	Yes	Fair	Unclear about measurement and reporting of sleep-related symptoms. Neither participants nor providers blind to group assignment; some difference in attrition but minimal.

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

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
Quinnell, 2014[215] 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 were not high).
Redline, 1998[189]	Yes	No	NR	NR	Yes	Excluded but examined in sensitivity analyses	Yes	Fair	Methods of allocation concealment NR; no masking reported.
Robinson, 2006[154]	Yes	Yes	Yes	Yes	Yes	None, excluded	Yes	Fair	Method of random sequence generation NR; missing data were excluded from analysis.
Ruttanaum-pawan, 2008[190] Kaneko, 2003[191]	Yes	No	No	Yes	Yes	NA	Yes	Fair	Open-label trial, 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.
Salord, 2016[192]	Yes	No	No	No	Yes	Dropped	ITT	Good	Unsure about management of missing data
Schwarz, 2018[291]	Yes	Yes	NA	Yes	Uncertain	Excluded	No (only analyzed those in the NIRS substudy who also had complete data for certain outcomes)	Poor	High risk of bias due to attrition, missing data, and methods of handling missing data; ESS is the eligible outcome for our purposes (the trial focused more so on outcomes that we're not looking at, such as measures of cerebral tissue oxygenation).
Shaw, 2016[193]	Yes	No	No	Yes	Yes	LOCF and imputation	Yes	Fair	Low attrition but significant differential attrition (14%) due to treatment intolerance in the intervention arm. Low adherence to intervention. Missing data addressed by LOCF and imputation.
Siccoli, 2008[155]	Yes	Yes	Yes	Yes	Yes	ITT: LOCF	Yes	Fair	Methods of randomization and allocation concealment NR.

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

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
Smith, 2007[156]	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[194]	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.
Traaen, 2021[199]	Yes	No	No	Partially	No	ITT	Yes	Fair	This study had decent adherence and very little missing data, so lack of a sensitivity analysis is not concerning. It is mildly underpowered given lower incidence of AF episodes than expected. They did not use sham CPAP, so the study is not blinded.
Weaver, 2012[157] CATNAP	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.
Weinstock, 2012[201] Redline, 2014[220]	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[158] West, 2009[159]	Yes	Yes	Yes	Yes	Yes	Excluded	Partially	Fair	Missing data excluded; consider assessors blinded because outcomes of interest were all patient reported.

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

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
Wimms, 2020[195] MERGE	Yes	No	No	No	Yes	LOCF	Yes	Fair	Patients and providers were unable to be masked. Does not look like assessors were masked; some if not all measures were self-reported.
Zhao, 2017[196] BestAIR	Yes	Partially (CPAP vs. sham masked, but other tx arms unable to be masked)	No	Partially (yes for nonpatient-reported outcomes)	Yes	NR	Yes	Fair	Providers unable to be masked, attrition, no information on how missing data were handled. Groups were comparable but no information provide on whether they were significant differences between groups.

* Answered using the study's ClinicalTrials.gov page: https://clinicaltrials.gov/ct2/show/NCT01901055.

Abbreviations: AHI=apnea-hypopnea index; APPLES=Apnea Positive Pressure Long-term Efficacy Study; BestAIR=Best Apnea Interventions for Research; BL=baseline; BMI=body mass index; BOCF=baseline observation carried forward; BP=blood pressure; CATNAP=CPAP Apnea Trial North American Program; CGM=continuous glucose monitoring; CPAP=continuous positive airway pressure; CV=cardiovascular; ESS=Epworth Sleepiness Scale; G=group; GEE=generalized estimating equation; HeartBEAT=Heart Biomarker Evaluation in Apnea Treatment; HTN=hypertension; ITT=intention to treat; KQ=key question; LOCF=last observation carried forward; MAD=mandibular advancement device; MOSAIC=Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular; N=number; NA=not applicable; NIRS=near-infrared spectroscopy; NR=not reported; OSA=obstructive sleep apnea; pbo=placebo; PG=polygraphy; PSG=polysomnography; pts=patients; QSQ=Quebec Sleep Questionnaire; RCT=randomized, controlled trial; RICCADSA=Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA; ROB=risk of bias; TOMADO=Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea-hypopnoea; tx=treatment; vs.=versus.

For RCTs and cohorts, definition of ratings based on below criteria:
Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with 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. Intention-to-treat analysis is used for RCTs.
Poor: Studies are graded "poor" if any of the following fatal flaws 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. Intention-to-treat analysis is lacking for RCTs.

Appendix D Table 7. Quality Ratings of Randomized, Controlled Trials of Interventions for OSA That Reported Harms (KQ 6)

First Author, Year Trial Name	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[206] Nikolopoulou, 2020[207]	NR	NR	NR	Yes	Fair	Methods NR, but they reported a lot of harms information.
Aarab, 2020[287]	Yes	Yes	Unclear	Yes	Poor	High attrition, inappropriate statistical methods, no adjustment for potential confounders.
Bloch, 2000[209]	NR	NR	NR	Yes	Fair	No information on harms assessment, but it looks like they did gather some harms information.
Durán-Cantolla, 2015[210]	NR	Partially	NR	Yes	Fair	No description of methods for harms assessment.
Engleman, 1999[171]	NR	NR	NR	Yes	Fair	No description of methods for harms assessment, but they recorded many.
Gagnadoux, 2017[216]	Yes	Yes	Yes	Yes	Fair	Some baseline differences that may have introduced bias: significantly more women in the MAD arm, and more than twice as many current smokers in the sham arm as the MAD arm (difference nearly significant).
Hui, 2006[137]	NR	NR	NR	Yes	Fair	Only harm reported was withdrawal due to adverse effects (discomfort).
Johnston, 2002[214]	Yes	Partially	NR	Yes	Fair	
Kushida, 2012[141] Batool-Anwar, 2016[142] APPLES	NR	NR	Yes (equal); NR for valid and reliable	Yes	Fair	
Lam, 2007[177]	NR	Partially	NR	Yes	Fair	Page 355: "Side effects of treatment were evaluated by self-reporting using questionnaires in a clinical setting." Implied prespecification and definition.
Malow, 2008[219]	NR	Partially	NR	Yes	Fair	
Marklund, 2015[217]	Yes	Yes	Yes	Yes	Fair	
Naismith, 2005[211] Gotsopoulos, 2002[212] Gotsopoulos, 2004[213]	Partially	Yes	Unclear	Yes	Fair	Gotsopoulos, 2002, page 744: "A self-administered detailed, in-house questionnaire was used to document … treatment-related side effects …"

Appendix D Table 7. Quality Ratings of Randomized, Controlled Trials of Interventions for OSA That Reported Harms (KQ 6)

First Author, Year Trial Name	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
Peker, 2016[185] Balcan, 2019[186] Celik, 2021[187] Celik, 2021[198] Wallstrom, 2019[200] RICCADSA	Unclear	Unclear	Unclear	Unclear	Poor	No information provided in article or on clinicaltrials.gov on whether harms and adverse events were prespecified, defined, or ascertainment.
Petri, 2008[218]	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[215] TOMADO	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[189]	NR	NR	NR	Yes	Fair	No information on harms assessment, but it looks like they did gather a lot of harms information based on the results reported.
Shaw, 2016[193]	NR	NR	Probably	Yes	Fair	No description of measurement in methods, but broad harms are reported in results and compared between treatment and control groups post hoc.
Smith, 2007[156]	NR	NR	NR	Yes	Fair	No information on harms assessment, but it looks like they did gather a lot of harms information based on the results reported.
Weaver, 2012[157] CATNAP	NR	NR	NR	Yes	Fair	Methods NR, but they reported a lot of harms information.
Weinstock, 2012[201] Redline, 2014[220]	NR	NR	Probably	Yes	Fair	Various harms of PAP and Sham PAP reported for both groups, no description of how harms were measured in methods.

Abbreviations: APPLES=Apnea Positive Pressure Long-term Efficacy Study; CATNAP=CPAP Apnea Trial North American Program; KQ=key question; MAD=mandibular advancement device; OSA=obstructive sleep apnea; NR=not reported; RICCADSA=Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA; TOMADO=Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea-hypopnoea.

Appendix E Table 1. Summary of Included Systematic Reviews and Meta-Analyses on Benefits of Treatment on AHI and Blood Pressure (KQ 4)

Author, Year	Intervention vs. Comparison	N Included Trials (Search Date)	Characteristics of Trials*	Pooled Results; N Trials (Participants); Heterogeneity
de Vries, 2018[123]	Oral appliance vs. inactive control	11 (December 31, 2016)	Mean Age: 45.7–58 % Female: 17–22 Race/Ethnicity: NR Mean BMI: 27.4–30.6 Mean AHI: 13.8–42.3 Mean ESS: NR OSA Severity: Any† % HTN: 19–89‡ % HF: NR	Mean Change (95% CI) Daytime SBP: -1.55 (-4.65 to 4.25); 5 (469); I^2=0% Daytime DBP: -1.14 (-2.78 to 3.38); 5 (469); I^2=0%
			Mean Age: 46.4–58 % Female: 17–21 Race/Ethnicity: NR Mean BMI: 28.4–31 Mean AHI: 21.5–42.3 Mean ESS: NR OSA Severity: Any† % HTN: 15–89‡ % HF: NR	Mean Change (95% CI) 24-Hour SBP: -1.38 (-3.41 to 0.64); 4 (427); I^2=0% 24-Hour DBP: -1.18 (-2.63 to 0.27); 4 (427); I^2=0%
Labarca, 2021[124]	CPAP vs. control in populations (sham CPAP, usual care)	8 (March 2020)	Mean Age: 57.2–61.2 % Female: 13.5–62.5 Race/Ethnicity: NR Mean BMI: 28.6–34.3 Mean AHI: 20–59.8 Mean ESS: 6.4–10 OSA Severity: NR % HTN: 100% % HF: NR	Mean Difference (95% CI) 24-Hour SBP: -5.06 (-7.98 to -2.13); 8 (606); I^2=69% 24-Hour DBP: -4.21 (-6.50 to -1.93); 7 (550); I^2=81% Daytime SBP: -2.34 (-6.94 to 2.27); 6 (526); I^2=84% Daytime DBP: -2.14 (-4.96 to 0.67); 6 (526); I^2=78% Nighttime SBP: -4.15 (-7.01 to -1.29); 6 (526); I^2=43% Nighttime DBP: -1.95 (-3.32 to -0.57); 6 (526); I^2=0%

Appendix E Table 1. Summary of Included Systematic Reviews and Meta-Analyses on Benefits of Treatment on AHI and Blood Pressure (KQ 4)

Author, Year	Intervention vs. Comparison	N Included Trials (Search Date)	Characteristics of Trials*	Pooled Results; N Trials (Participants); Heterogeneity
Patil, 2019[125]	PAP vs. inactive control (sham, usual care, oral pbo)	184 (February 2018)	Mean Age: NR % Female: NR Race/Ethnicity: NR Mean BMI: NR Mean AHI: NR Mean ESS:NR OSA Severity: NR % HTN: NR % HF: NR	Mean Difference (95% CI) All Participants[§] AHI, events/hour: -23.41(-28.51 to -18.30); 11 (832); I^2=93% Nighttime SBP: -4.21 (-5.96 to -2.45); 14 (1,272); I^2=9% Nighttime DBP: -2.31 (-3.72 to -0.91); 15 (1,451); I^2=41% Daytime SBP: -2.76 (-4.31 to -1.20); 12 (1,191); I^2=5% Daytime DBP: -1.98 (-3.02 to -0.93); 12 (1,191); I^2=4% 24-Hour SBP: -1.47 (-2.28 to -0.66); 23 (4,905); I^2=0% 24-Hour DBP: -1.58 (-2.23 to -0.93); 22 (4,595); I^2=6% Mean 24-Hour BP: -2.63 (-3.86 to -1.39); 8 (994); I^2=0% Resistant Hypertensive[‖] Nighttime SBP: -3.26 (-6.11 to -0.41); 5 (446); I^2=0% Nighttime DBP: -2.20 (-4.39 to -0.01); 5 (444); I^2=0% Daytime SBP: -1.54 (-4.47 to 1.39); 4 (409); I^2=0% Daytime DBP: -1.13 (-3.37 to 1.12); 4 (409); I^2=0% 24-Hour SBP: -2.15 (-5.05 to 0.75); 4 (409); I^2=0% 24-Hour DBP: -2.06 (-4.12 to -0.00); 4 (409); I^2=0% Hypertensive Nighttime SBP: -3.94 (-6.46 to -1.43); 2 (530); I^2=0% Nighttime DBP: -3.03 (-5.28 to -0.79); 2 (530); I^2=45% Daytime SBP: -2.70 (-4.92 to -0.47); 2 (530); I^2=0% Daytime DBP: -2.40 (-3.88 to -0.92); 2 (530); I^2=0% 24-Hour SBP: -2.53 (-4.30 to -0.76); 5 (986); I^2=0% 24-Hour DBP: -2.23 (-3.42 to -1.03); 5 (986); I^2=0% Mean 24-Hour BP: -2.16 (-3.59 to -0.72); 4 (627); I^2=0%
Zhang, 2016[126]	CPAP vs. control Eligibility limited to trials enrolling populations with minimally symptomatic, asymptomatic, or nonsleepy OSA	7 (April 1, 2016)	Mean Age: 51.9–66.0 % Female: 9–24 Race/Ethnicity: NR Mean BMI: 28.5–33.2 Mean AHI: 28.8–55.4 Mean ESS:4.6–7.95 OSA Severity: NR % HTN: 24.5–77 % HF: NR	Mean Difference (95% CI) SBP: -0.51 (-3.39 to 2.38); 5 (1,541); I^2=84% DBP: -0.92 (-1.39 to -0.46); 5 (1,541); I^2=0.0% AHI or ODI: -15.57 (-29.32 to -1.82); 3 (1,541); I^2=87.2%

* Characteristics are for all included studies in the reviews, not limited to the subset that report on AHI or blood pressure outcomes.

[†] Three studies reporting on BP outcomes enrolled populations with mild-severe OSA, and one each enrolled populations with moderate to severe and mild to moderate.

[ǂ] Defined as the proportion who were on blood pressure medication.

[§] This includes mixed populations of normotensives and hypertensives, many treated with antihypertensive medications.

[‖] Defined as participants treated with ≥3 antihypertensive medications.

Appendix E Table 1. Summary of Included Systematic Reviews and Meta-Analyses on Benefits of Treatment on AHI and Blood Pressure (KQ 4)

Abbreviations: AHI=apnea-hypopnea index; BMI=body mass index; BP=blood pressure; CI=confidence interval; CPAP=continuous positive airway pressure; DBP=diastolic blood pressure; ESS=Epworth Sleepiness Scale; HF=heart failure; HTN=hypertension; KQ=key question; N=number; NR=not reported; ODI=oxygen desaturation index; OSA=obstructive sleep apnea; PAP=positive airway pressure; pbo=placebo; SBP=systolic blood pressure; vs.=versus.

Appendix E Table 2. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Sham CPAP (KQs 5 and 6)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Weeks	Mean (Range) Age	% F	Race/ Ethnicity %	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Benefits 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
Barbe, 2001[127] Parallel	nCPAP (29) Sham CPAP (26)	Sleep clinic	No	Spain	6	53	9	NR	29	54–57	7	Severe only	NR; 0	Fair
Campos-Rodriguez, 2006[129] Parallel	CPAP (36) Sham CPAP (36)	Sleep center	No	Spain	4	57	40	NR	34–36	58–60	14–15	Mild to severe	100%; NR†	Fair
Chasens, 2014[130] Parallel	CPAP (12) Sham CPAP (11)	Community	No	United States	4	56	39	Black/ biracial: 52	36	39	11	Mod to severe	NR; NR	Fair
Chong, 2006[131] Parallel	CPAP (19) Sham CPAP (20)	Ads, referrals	No	United States	3	78	26	Non-Caucasian: 5	24–25	RDI 26–31	8–9	Mild to severe	NR; 0	Fair
Coughlin, 2007[132] Cross-over	Total (35) CPAP first (18) Sham first (17)	Sleep center	No	United Kingdom	6 active; 6 sham	49	0	NR	36	RDI 40	14	Mod to severe	79; 0	Good
Durán-Cantolla, 2010[133] Parallel	CPAP (169) Sham (171)	Referrals to 11 general hospitals	No	Spain	12	52	19	NR	32	43–45	10	Mod to severe	100 per GP, but 64 vs. 56 from ABPM; NR	Good
Egea, 2008[134] Parallel	Overall‡ CPAP (35) Sham CPAP (38)	Referral from cardiology to sleep center	No	Spain	12	63	4–9	NR	31–32	41–43	7–8	Mild to severe	NR; 100	Fair
Haensel, 2007[135] Parallel	CPAP (25) Sham CPAP (25)	Ads, word of mouth, referrals	No	United States	2	49	20	White: 60 Black: 12 Hispanic: 12 Asian: 6 Other: 10	33	58–64	NR	Mod to severe	14; 0	Fair
Hoyos, 2012[136] Parallel	CPAP (34) Sham CPAP (31)	Sleep clinics	No	Australia	12	49	0	NR	31–32	39–42	10	Mod to severe	34; NR	Fair

Appendix E Table 2. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Sham CPAP (KQs 5 and 6)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Weeks	Mean (Range) Age	% F	Race/ Ethnicity %	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Benefits Quality
Hui, 2006[137] 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[138] Hack, 2000[139] Parallel	nCPAP (54) Sham nCPAP (53)	Referred to sleep clinic	No	United Kingdom	4	Median 48–50 (33–71)	0	NR	35	ODI (>4%): Median 36–38	Median 16–17	Mild to severe	19; NR	Fair
Jones, 2013[140] Cross-over	Total (53)[§] CPAP first (25) Sham CPAP first (27)	Sleep medicine department	No	United Kingdom	12 CPAP; 12 sham	46	35	NR	Med-ian 30	Median 31	Median 13	Mod to severe	NR; NR	Fair
Kushida, 2012[141] Batool-Anwar, 2016[142] Parallel APPLES	CPAP (558) Sham (547)	Sleep clinics (5 hospitals)	No	United States	24	52	35	White: 76 Non-White: 24	32	40–41	10	Mild to severe	NR; 0	Fair
Lam, 2010[143] 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[144] Parallel	Total (38) CPAP (17) Sham CPAP (21)	Ads and word of mouth	No	United States	3	47	NR	African American: 8 White: 89 Other: 3	28–29	29–33	7–10	Mild to severe	5; 0	Fair
Loredo, 2006[145] 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[219] Parallel	Total (35) CPAP (22) Sham CPAP (13)	Epilepsy clinic	No	United States	10	42	43	NR	32–35	16–19	NR	Mild to severe	22%; NR	Fair
Marshall, 2005[146] 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	22	13	Mild to mod	NR; NR	Good
Melehan, 2018[147] Parallel	CPAP (31) Sham CPAP (30)	NR	No	Australia	12	54	0	NR	33	44–48	10	Severe only	47–58; NR	Fair
Montserrat, 2001[148] Parallel	CPAP (24) Sham CPAP (24)	Sleep clinic	No	Spain	6	54	NR	NR	30–34	54	16–17	Moderate to severe	NR; 0	Fair

Appendix E Table 2. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Sham CPAP (KQs 5 and 6)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Weeks	Mean (Range) Age	% F	Race/ Ethnicity %	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Benefits Quality
Neikrug, 2014[149] Parallel	CPAP (19) Sham nCPAP (19)	Neurologist†† referral and volunteer	No	United States	3	67	32	NR	27–28	22	NR	Mild to severe	NR; NR	Fair
Nguyen, 2010[150] Parallel	nCPAP (10) Sham nCPAP (10)	Sleep clinic	No	United States	12	53	10	Non-Caucasian: 40	30	32–39	NR	Mod to severe	100; 0	Fair
Pepperell, 2002[151] Kohler, 2008[152] Parallel	CPAP (59) Sham CPAP (59)	Referred by ENTs, GPs, or consultants	No	United Kingdom	4	51	0	NR	35	NR	16	Mild to severe	19; NR	Fair
Phillips, 2011[153] 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
Robinson, 2006[154] 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	Mild to severe	100; NR	Fair
Siccoli, 2008[155] 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[156] 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[157] Parallel CATNAP	CPAP (141)§§ Sham CPAP (140)	Respiratory Clinics	No	United States and Canada	8	51	37–45	African American: 16–17[lll]	33–34	13	15	Mild to mod	40; 2	Fair
Weinstock, 2012[201, 220] Cross-over	Total (50) CPAP first (25) Sham CPAP first (25)	Sleep clinics, prior studies and ads	No	United States	8 active; 8 sham	54	58	Black: 40	38–39	32–44	NR	Mod to severe	NR; NR	Fair
West, 2007[158] West, 2009[159] Parallel	CPAP (21) Sham CPAP (21)	Sleep center	No	United Kingdom	12	56	0	NR	37	NR	14–15	Mild to severe	NR; NR	Fair

† 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).

§One person dropped out before beginning a treatment, but unclear if it was before or after randomization and unclear which group they were in.

l Forty-eight 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.

Appendix E Table 2. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Sham CPAP (KQs 5 and 6)

[**] Study also had a sham+oxygen arm (17).
[††] Patients with Parkinson's disease.
[#] 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 as follows: active CPAP=121; sham CPAP=118. All characteristics are for those randomized and exposed.
[ll] These percentages are based on the sample of randomized and exposed participants, not the original N randomized of 281.

Abbreviations: ABPM=ambulatory blood pressure monitor; AHI=apnea-hypopnea index; APPLES=Apnea Positive Pressure Long-term Efficacy Study; BMI=body mass index; CATNAP=CPAP Apnea Trial North American Program; 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; KQ=key question; 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; pts=patients; RDI=respiratory disturbance index.

Appendix E Table 3. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Control (KQs 5 and 6)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Weeks	Mean (Range) Age	% F	Race/ Ethnicity %	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Benefits Quality
Ballester, 1999[160] Parallel	CPAP (68) Usual care (37)	NR	No	Spain	12	53	12	NR	32	56	12	Mod to severe	NR; NR	Fair
Banghøj, 2021[161] Parallel	CPAP (36) Control (36)	Hospitals	No	Denmark	12	63	22	NR	33–36	35	7	Mod to severe	NR; NR	Fair
Barbe, 2010[162] 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[163] Parallel	CPAP (357) Control (366)	Teaching hospitals	No	Spain	Median 208*	52	14	NR	31	Median 35–42	7	Mod to severe	50–53; NR	Fair
Barnes, 2004[164] Cross-over	CPAP (97)† Pbo (98)	Referrals	No	Australia	12 active; 12 pbo	47	20	NR	31	21	11	Mild to mod	15; NR	Fair
Campos-Rodriguez 2016[165] Parallel	CPAP (151) Control (156)	Sleep centers	No	Spain	12	57	100	NR	34	32	10	Mod to severe	NR; NR	Fair
Craig, 2012[166] Parallel MOSAIC	CPAP (195) Standard care‡ (196)	Sleep clinics	No	United Kingdom and Canada	24	58	22	NR	32–33	ODI >4% dips/ hour: Median 9–10	8	NR§	76–77; NR	Fair
Dalmases, 2015[167] Parallel	CPAP (17) Conservative (16)	Hospital	Yes	Spain	12	71	30	NR	31	56	6–8	Severe only	85; NR	Fair
Engleman, 1994[168] Cross-over	Total (35)¶ CPAP first (17) Oral pbo 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[169] Cross-over	Total (18) CPAP first (10) Oral pbo 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[170] Cross-over	Total (23) CPAP first (10) Pbo (13)	Sleep center	No	United Kingdom	4 active; 4 pbo	47	9	NR	30	43	12	Mod to severe	NR; NR	Fair

Appendix E Table 3. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Control (KQs 5 and 6)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Weeks	Mean (Range) Age	% F	Race/ Ethnicity %	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Benefits Quality
Engleman, 1999[171] Cross-over	Total (37) CPAP first (NR) Oral pbo first (NR)	Sleep clinic	No	United Kingdom	4 active; 4 pbo	44	38	NR	30	10	13	Mild only	NR; NR	Fair
Faccenda, 2001[172] 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	Medi-an 30	Median 35	Median 15	Mod to severe	0; NR	Fair
Gottlieb, 2014[173] Lewis, 2017[174] Parallel HeartBEAT	CPAP+usual care‖ (106) Usual care alone (106)¶	Cardiology practices	Yes, Berlin#	United States	12	63	26	Caucasian: 83–86 Black: 7–12 Asian: 2–3 Other: 3–6	34	25	8–10	Mod to severe	89; NR	Good
Jackson, 2021[175] Jackson, 2019[176] Parallel	CPAP (82) Wait-list (39)	Sleep clinic	No	Australia	16	52	42	NR	35	NR	8	Mild to severe	NR; NR	Fair
Lam, 2007[177] Parallel	CPAP (34)** Usual care (33)††	Sleep center	No	Hong Kong	10	46	21	NR	27	21	12	Mild to severe	19; NR	Fair
Lim, 2007[178] Parallel	nCPAP (17) Sham CPAP (14)	Ads, word of mouth, referrals	No	United States	2	48	NR	NR	31–32	64–66	11–13	Mod to severe	NR; 0	Fair
Lui, 2020[179] Parallel	CPAP (45) Control (45)	Sleep clinics	No	Hong Kong	4	47	18	NR	30	58	11	Severe only	NR; NR	Fair
Martinez-Garcia, 2013[180] 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
Martinez-Garcia, 2015[181] Parallel	CPAP (115) No CPAP (109)	Sleep lab and centers	No	Spain	12	76	32	NR	33	50	10	Severe only	80; NR	Fair
Masa, 2015[182] Parallel Pickwick	Total (150) CPAP (80) Lifestyle modification control (70)	Hospitals	Yes	Spain	8	60	47–56	NR	44–45	69–71	11	Severe only	62-65; 13-16	Fair

Appendix E Table 3. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Control (KQs 5 and 6)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Weeks	Mean (Range) Age	% F	Race/ Ethnicity %	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Benefits Quality
McArdle, 2001[183] 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[184] Parallel PREDICT	CPAP + best supportive care (BSC) (140) BSC only (138)	Sleep centers (14)	No	United Kingdom	52	71	18	White: 96 Asian: 3 Other: 1	34	ODI (>4% dips per hour): 28–29	12	Mild to severe	73; 6	Good
Ng, 2018[197] Parallel	CPAP (17) Conservative treatment (20)	Hospital respiratory clinic	No	Hong Kong	12	52	53–80	NR	26–28	19–22	8–10	Mild to severe	NR; NR	Fair
Peker, 2016[185-187, 198, 200] Parallel RICCADSA	Total (244) CPAP (122) No CPAP (122)	Hospitals	Yes	Sweden	312	66	14–18	NR	28–29	28–29	6	Mod only	59–69; NR	Fair
Ponce, 2019[188] Parallel	CPAP (73) No CPAP (72)	Teaching clinical center	No	Spain	12	75	35§§	NR	30	22	9	Mod only	NR; NR	Fair
Redline, 1998[189] Parallel	nCPAP (59) Conservative therapy‖‖ (52)	Ads and referrals	No	United States	8–12	48	48	Non-European American (majority African American): 38 European American: 62	32–33	RDI 13	10–11	Mild to mod	NR; 0	Fair
Ruttanaum-pawan, 2008[190] Kaneko, 2003[191] Parallel	CPAP (19) Usual care (14)	HF clinic	Yes, ESS	Canada	4	60	9	NR	30–32	36–51	NR	Mod to severe	42–58; 100	Fair
Salord, 2016[192] Parallel	CPAP (42) Conservative (38)	Sleep clinics	No	Spain	12	47	73	NR	47	56	8	Severe only	NR; NR	Good
Shaw, 2016[193] Parallel	CPAP+usual care (151) Usual care (147)	Hospitals and specialist clinics	No	Australia and North America	24	62	36	White: 84 Black: 6 Hawaiian/Pacific Islander: 1 Asian: 8 Other or unknown: 1	33	26–28	9–10	Mod to severe	NR; NR	Fair

Appendix E Table 3. Characteristics of Included Randomized, Controlled Trials Comparing CPAP and Control (KQs 5 and 6)

First Author, Year Design Trial Name	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Weeks	Mean (Range) Age	% F	Race/ Ethnicity %	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Benefits Quality
Tomfohr, 2011[194] Parallel	CPAP (34) Pbo CPAP (37)	Ads and referrals	No	United States	3	48	14	Caucasian: 86 Asian: 2 African American: 10 Other: 2	29–31	32–39	9–11	Mild to severe	NR; NR	Fair
Traaen, 2021[199] Parallel A3	CPAP+usual care (55) Usual care (54)	Outpatient cardiology clinics	Yes	Norway	24	63	24	NR	29–30	Median 21–23	8	Mod to severe	39–43; NR	Fair
Wimms, 2020[195] Parallel MERGE	CPAP (115) Control (118)	Sleep centers	No	United Kingdom	12	50	31	White: 89 Non-White: 11	30	Median 10–11	10	Mild only	24–33; NR	Fair
Zhao, 2017[196] Parallel BestAIR	CPAP (83) Control (86)	Outpatient clinic	No	United States	48	64	35	White: 89 Black: 7 Hispanic: 4 Other: 4	32	29	8–9	Mod to severe	85; NR	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 six different orders were possible, they did not list out individuals' actual order. Numbers represent the number of people who started treatment in that arm (104 participants total; 80 completed all three arms).
ǂ One followup visit with a physician between randomization and the final visit at 6 months.
§ Had to have >7.5 oxygen desaturations per hour of >4%, but had insufficient daytime symptoms associated with OSA to warrant CPAP therapy. This was made based on discussion with physician based on benefits of CPAP vs. potential lifelong nightly usage of CPAP.
ǁ Usual care was defined as "healthy lifestyle and sleep education."
¶ Study also included an oxygen plus 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 included a MAD arm.
†† Authors defined as "mild to moderate," but allowed AHI up to 40, and the range of included patients included some with severe OSA.
‡‡ BP remained above goal despite treatment with 3 or more antihypertensive medications.
§§ We used the data from Table 1 and not the text of the publication. There was a discrepancy between the two.
‖ Conservative therapy for all patients consisted of sleep hygiene counseling, weight loss referrals for patients who were overweight, and nasal steroid spray for those with nasal congestion. Control participants also received nasal dilator strips.

Abbreviations: A3=Atrial Fibrillation, Apnea, Airway Pressure; AHI=apnea-hypopnea index; BestAIR=Best Apnea Interventions for Research; BMI=body mass index; BP=blood pressure; 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; IQR=interquartile range; KQ=key question; MAD=mandibular advancement device; mod=moderate; MOSAIC=Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular; 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; RICCADSA=Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA; tx=treatment.

Appendix E Table 4. 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 (27) nCPAP first (14) Sham nCPAP first (13)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Ballester, 1999[160]	CPAP (68) Usual care (37)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Banghøj, 2021[161]	CPAP (36) Control (36)	0 (0.0) 1 (2.8)	NR	NR	NR	NR	NR	NR	NR
Barbe, 2001[127]	Total (55) CPAP (29) Sham CPAP (26)	0 (0.0) 0 (0.0)	FOSQ, mean (SE) BL CPAP: 102 (3) Sham: 107 (3) 6 weeks CPAP: 108 (2) Sham: 110 (2) Change from BL CPAP: 7 (2) Sham: 3 (3) Between-group diff: p>0.2 SF-36 PCS, mean (SE) BL CPAP: 49 (1) Sham: 48 (1) 6 weeks CPAP: 51 (1) Sham: 50 (1) Change from BL CPAP: 2 (1) Sham: 1 (1) Between-group diff: p>0.2	Hits on SteerClear test, mean (SE) % Baseline CPAP: 5 (1) Sham: 6 (2) 6 weeks CPAP: 4 (1) Sham: 5 (2) Change from BL CPAP: -1 (1) Sham: -1 (1) Between-group diff: p>0.2 Also reported: WAIS digit symbols, block design, digit span, PASAT 1-4, Trail Making test A and B, Wechsler memory scale	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Barbe, 2001[127] (continued)			SF-36 MCS, mean (SE) BL CPAP: 51 (2) Sham: 50 (2) 6 weeks CPAP: 51 (2) Sham: 52 (2) Change from BL CPAP change: -1 (2) Sham change: 1 (2) Between-group diff: p>0.2						
Barbe, 2012[163]	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) Nonfatal stroke: 3 (0.8) 2 (0.5)	3 (0.8) 5 (1.4)	NR

Appendix E Table 4. 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 (%)
Barnes, 2004[164]	CPAP (97) Pbo (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. pbo; p<0.05	Reported: Word Pair Memory Recall; Logical Memory Test; Digit Span Backwards; Trail Making B; Digit Symbol Substitution Task; COWAT; PVT; Stroop Color Association Test	NR	NR	NR	NR	NR
Campos-Rodriguez 2016[165]	CPAP (151) Control (156)	NR	SF-12 Physical, between-group diff (95% CI): 2.78 (0.96 to 4.61), p=0.003 SF-12 Mental, between-group diff (95% CI): 1.27 (-1.01 to 3.56), p=0.27 Reports QSQ hyper-somnolence, diurnal symptoms, nocturnal symptoms, emotions, and social interaction	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Craig, 2012[166] MOSAIC	CPAP (195) Standard care (196)	1 (0.5) 0 (0.0)	MCS, Mean (SD) BL: 48.2 (10.4) 46.6 (11.3) 24 weeks: 52.0 (9.8) 48.5 (11.0) Between-group diff: 2.6 (95% CI, 0.9 to 4.2; p=0.003) EQ-5D score, Mean (SD)‡ BL: 0.80 (0.17) 0.75 (0.24) 24 weeks: 0.83 (0.19) 0.80 (0.22) Between-group diff: +0.20 (95% CI, -0.03 to 0.06; p=0.43) SAQLI, mean (SD) BL: 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 diff: p<0.0001	NR	NR	Angina: 1 (0.6) 3 (1.7) MI: 0 (0.0) 0 (0.0) PVD: 2 (1.2) 1 (0.6) AF: 6 (3.5) 7 (4.1)	TIA: 1 (0.6) 0 (0.0) Stroke: 0 (0.0) 0 (0.0)	NR	NR

Appendix E Table 4. 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 (%)
Dalmases, 2015[167]	CPAP (17) Conservative (16)	NR	Reports QSQ total, sleepiness, diurnal symptoms, nocturnal symptoms, emotions, and social interaction scores	Reports RAVLT, Digit Span Forward, Digit Span Backward, Digit symbol, Trail Making A, Trail Making B, Semantic Fluency, Phonemic fluency	NR	NR	NR	NR	NR
Durán-Cantolla, 2010[133]	CPAP (169) Sham (171)	0 (0.0) 0 (0.0)	EuroQol, mean (SD) at baseline, 6 weeks, 12 weeks CPAP 69 (15), 74 (14),[§] 76 (16)[‖] Sham CPAP 72 (17), 72 (16), 73 (15)	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Egea, 2008[134]	CPAP¶ (35) Sham CPAP (38)	0 (0.0) 1 (2.6)	OSA Only SF-36 PCS, Mean (SE) BL: 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 diff: p=NS SF-36 MCS, Mean (SE) BL: 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 diff: p=NS	NR	NR	Angina 0 (0.0) 1 (2.6)	NR	NR	NR

Appendix E Table 4. 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, 1994[168]	CPAP first (17) Oral pbo first (15)	0 (0.0) 0 (0.0)	NHP-2, 4 weeks: 4.9 (SE 0.9) 7.9 (SE 0.9) Between-group diff; p=0.002 CPAP > pbo (p<0.05) for social life, sex life, and ability to carry out domestic chores	Mental flexibility (Trail Making 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; however, after adjustment for order effect, p=0.11	NR	NR	NR	NR	NR

Appendix E Table 4. 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[169]	CPAP first (8) Oral pbo first (8)	0 (0.0) 0 (0.0)	Nottingham Health Profile Part 2, total score 4 weeks 3.8 (SE 1.1) 5.8 (SE 1.4) Between groups p=NS	Reports IQ decrement, Trail Making, SteerClear, PASAT2, RVIPT, reaction time, verbal fluency, BVRT Only significant changes on Trail Making B; no changes on other various cognitive functioning measures	NR	NR	NR	NR	NR
Engleman, 1998[170]	CPAP first (10) Pbo (13)	0 (0.0) 0 (0.0)	NHP-2 Baseline, mean (SD) 8.0 (5.0) 4 weeks, 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-minute SteerClear; Trail Making 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[171]	Total (37) CPAP first (NR) Oral pbo first (NR)	0 (0.0) 0 (0.0)	NHP-2 score, mean (SD) Baseline: 10.5 (4.8)	SteerClear (obstacles hit), mean (SD) Baseline: 295 (183)	NR	NR	NR	NR	0 (0.0) 3 (8.8)

Appendix E Table 4. 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, 1999[171] (continued)			4 weeks CPAP: 6.1 (4.7) 4 weeks pbo: 7.3 (5.2) Between groups p=NS SF-36 Domains only: Physical Function Baseline: 75 (27) 4 weeks CPAP: 84 (22) 4 weeks pbo: 83 (23) Between groups p=NS Mental health Baseline: 64 (19) 4 weeks CPAP: 79 (16) 4 weeks pbo: 75 (15) Between groups p=NS General Health Baseline: 68 (21) 4 weeks CPAP: 76 (19) 4 weeks pbo: 74 (20) Between groups p=NS	4 weeks CPAP: 189 (156) 4 weeks pbo: 195 (158) Between groups p=NS Also reported Trail Making A, Trail Making B, Digit Symbol, Block Design, performance IQ, PASAT					

Appendix E Table 4. 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 (%)
Faccenda, 2001[172]	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[173] Lewis, 2017[174] HeartBEAT	CPAP+ usual care (106) Usual care alone (106)	0 (0.0) 0 (0.0)	SF-36 MCS, mean (SD) BL 48.9 (11) 48.9 (12.3) 12 weeks 52.6 (10) 49.7 (11) Within-group diff 3.7 (8.2), p=0.001 0.8 (8.1), p=0.3342 Between-group diff (95% CI): 2.88 (0.9 to 4.87), p=0.005	NR	0 (0.0) 0 (0.0)	Unstable angina: 0 (0.0) 1 (0.9) MI: 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

Appendix E Table 4. 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 (%)
Gottlieb, 2014[173] Lewis, 2017[174] HeartBEAT (continued)			SF-36 PCS mean (SD) BL 44.7 (9.5) 43.6 (9) 12 weeks 44.6 (10.2), p=0.8275 42.9 (9.3), p=0.2211 Within-group diff -0.1 (5.1), p=0.8275 -0.8 (6.4), p=0.2211 Between-group diff (95% CI): 0.86 (-0.77 to 2.49), p=0.3						
Haensel, 2007[135]	CPAP (25) Sham CPAP (25)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Jenkinson, 1999[138] Hack, 2000[139]	CPAP (54) Sub-therapeutic CPAP (53)	0 (0.0) 0 (0.0)	SF-36 MCS, mean (SD) BL: 44.8 (10.4) 43.5 (10.7) 4 weeks: 55.4 (7.0) 47.8 (10.1) Between-group diff: p=0.002 SF-36 PCS, mean (SD): BL: 43.7 (11.6) 42.6 (10.1) 4 weeks: 49.4 (10.1) 45.5 (10.4) 5.7 (NR); p<0.001 2.9 (NR); p=0.007 Between-group diff: p=0.080		NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Kushida, 2012[141] Batool-Anwar, 2016[142] APPLES	CPAP (558) Sham (547)	2 (0.4) 2 (0.4)	SAQLI, mean (SD) Compliance <4 hours BL: 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 BL: 4.7 (0.8) 4.8 (0.8) 6 months: 5.0 (0.7) 4.9 (0.7) Between-group diff: p<0.05	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 4. 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 (%)
Lam, 2007[177]	CPAP (34) Usual care (33)	0 (0.0) 0 (0.0)	SAQLI total score, mean (SE) BL: 5.0 (0.1) 5.1 (0.1) 10 weeks: 5.5 (0.1) 5.0 (0.1) Between-group diff: 0.77 (-1.5 to 0.4); p=0.04 SF-36, mean (SEM); p-value of within-group change from baseline; between-group diff 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)	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Lam, 2007[177] (continued)			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)						
Lee, 2011[144]	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 Visuospatial Memory Test-Rev; Hopkins Verbal Learning Test-Rev; Trail Making A/B; Digit Vigilance; Stroop Color-Word; Word Fluency	NR	NR	NR	NR	NR
Lim, 2007[178]	Total (46) nCPAP (17) Sham CPAP (14)	NR	NR	Reports multiple cognitive function outcomes	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Marshall, 2005[146]	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 Between-group diff 0.3 (-0.5 to 1.1) SF-36 domains Mental health Baseline: 75 (3) 77 (2) p=NS 80 (2) p<0.05 Between-group diff=-3 (-10 to 3)	Psychomotor vigilance task: Mean (SE) reaction time (ms): Baseline: 264 (5) 266 (5) p=NS 259 (5) p=NS Between-group 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 Between-group 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 Between-group diff=-0.1 (-2.0 to 1.9)	NR	Nonfatal MI: 0 (0.0) 1 (3.2)	NR	NR	NR
Martinez-Garcia, 2015[181]	CPAP (115) No CPAP (109)	NR	Reports QSQ hypersomnol-ence, diurnal symptoms, nocturnal symptoms, emotions, and social interaction	Reports digit span, digit symbol, Trail Making A, and Trail Making B	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Masa, 2015[182] Pickwick	Total (150) CPAP (80) Control (70)	NR	SF-36 MCS, mean (SD) BL: 42.0 (14.0) 44.0 (12.0) 8 weeks: 46.6 (NR) 45.2 (NR) Between-group diff: p=NS SF-36 PCS, mean (SD): Baseline: 36.0 (10.0) 37.0 (11.0) 8 weeks: 37.2 (NR) 37.2 (NR) Between-group diff: p=NS FOSQ total, mean (SD): BL: 71.0 (21.0) 77.0 (23.0) 8 weeks: 76.1 (NR) 75.3 (NR) Between-group diff: p=0.027	NR	NR	NR	NR	NR	0 NR

Appendix E Table 4. 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[184] PREDICT	Total (278) CPAP+BSC (140) BSC only (138)	NR	SAQLI, 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 reported 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 AF 6 (4.3) 12 (8.7) New PVD 1 (0.3) 0 (0.0) All 12 (4.3) 15 (10.1) between 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 all adverse CV events p=0.72	NR	
Melehan, 2018[147]	CPAP (31) Sham CPAP (30)	NR	Numerical data NR. Authors note that overall scores for SF-36 and FOSQ did not change in the CPAP group (intention-to-treat population).	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Montserrat, 2001[148]	CPAP (24) Pbo 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[149]	CPAP (19) Sham CPAP (19)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Ng, 2018[197]	CPAP (17) Conservative treatment (20)	NR	SF36 MCS, mean change from baseline (SD): 4.7 (22.9); p=NR -2.8 (12.6); p=NR Between groups p=0.243 SF36 PCS, mean change from baseline (SD): 8.8 (17.6); p=NR -0.8 (12.3); p=NR Between groups p=0.061	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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[150]	nCPAP (10), sham CPAP (10)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Peker, 2016[185-187, 198, 200] RICCADSA	Total (244) CPAP (122) Control (122)	7 (6) 9 (7)	SF-36 MCS, mean (SD) BL: 51.8 (9.2) 52.3 (9.4) 52 weeks: 54.2 (7.3) 52.1 (9.7) Between-group diff: p=NR SF-36 PCS, mean (SD): Baseline: 45.2 (9.3) 44.9 (9.6) 52 weeks: 44.1 (10.5) 45.4 (10.4) Between-group diff: p=NR	NR	NR	Total (repeat revascularization, acute MI, CV death, and acute hospital admissions for CVD) 61 (50) 61 (50) Repeat revascularization 17 (14) 14 (11) Acute MI 11 (9) 8 (7) CV death 3 (2) 7 (6)	Stroke 3 (2) 6 (5)	NR	NR
Phillips, 2011[153]	Total (37) CPAP first (18) Sham CPAP first (19)	NR	FOSQ total, mean (SD): Baseline: 15.2 (3.1) 8 weeks, mean (SE): 16.0 (0.53) 16.7 (0.52) Between groups p=0.056	NR	NR	NR	NR	NR	NR
Ponce, 2019[188]	CPAP (73) No CPAP (72)	NR		Also reported digit span and symbol test	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Redline, 1998[189]	Total (111) nCPAP (59) Conservative therapy (52)	0 (0.0) 0 (0.0)		NR	NR	NR	NR	NR	NR
Robinson, 2006[154]	Total (35) CPAP first (18) Sham first (17)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Ruttanaum-pawan, 2008[190] Kaneko, 2003[191]	CPAP (12) No treatment (12)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	All pts had HF	NR
Siccoli, 2008[155]	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 76.8 (16.2) p<0.0001 68.6 (22.7) p=0.17 Between groups p=0.002	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Siccoli, 2008[155] (continued)			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						
Shaw, 2016[193]	CPAP (151) Control (147)	NR	SF-36 MCS, mean (SD) BL: 50 (11.3) 50.9 (10) 24 weeks: 52.6 (10.1) 51.8 (10.3) Between-group diff 1.5 (SD -0.7 to 3.7)	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Smith, 2007[156]	Total (24) CPAP first (11) Sham first (13)	0 (0.0) 0 (0.0)	MLHF Baseline: 38 (27) G1: 36 (29) G2: 34 (28) Between-group difference 1.0 (-4.3 to 6.4) p=0.70 SF36 PCS Baseline: 34 (16) G1: 34 (14) G2: 35 (14) Between-group diff -1.0 (-3.6 to 1.6); p=0.43 SF36 MCS BL: 51 (10) G1: 49 (12) G2: 50 (11) Between-group diff -0.5 (-4.2 to 3.2); p=0.79	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Traaen, 2021[199] A3	CPAP+usual care (54) Usual care (54)	NR	FOSQ Baseline G1: 17.4 (1.9) G2: 17.7 (2.0) 6 months G1: 17.6 (2.0) G2: 17.7 (2.0) Between-group difference in mean change from BL (95% CI): 0.1 (-0.5 to 0.6); p=0.850 SF-36 PCS Baseline G1: 43.1 (9.1) G2: 43.3 (10.2) 6 months G1: 43.6 (10.2) G2: 45.9 (9.6) Between-group difference in mean change from BL (95% CI): -2.1 (-5.1 to 0.8); p=0.160 SF-36 MCS Baseline G1: 49.9 (9.5) G2: 52.8 (6.6) 6 months G1: 52.5 (8.7) G2: 51.5 (8.8) Between-group difference in mean change from BL (95% CI): 2.8 (-0.1 to 5.8); p=0.058	NR	NR	Pacemaker implantation due to syncope and prolonged pauses G1: 2 (4) G2: 0	Hemorrhagic stroke G1: 0 G2: 1 (2)	NR	NR

Appendix E Table 4. 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 (%)
Weaver, 2012[157] CATNAP	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 from BL (SE); 0.95 (0.34) Between-group diff p=0.006 SF-36, PCS Adj mean change from BL: 3.89 0.04 Adj between-group diff in mean change from BL (SE): 3.85 (1.17) 95% CI, 1.53 to 6.17 p=0.001 SF-36, MCS Adj mean change from BL: 3.07 2.21 Adj between-group diff in	NR	NR	NR	NR	NR	NR

Appendix E Table 4. 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 (%)
Weaver, 2012[157] CATNAP (continued)			mean change from BL (SE): 0.86 (1.42) 95% CI, -1.95 to 3.67 p=0.546						
West, 2007[158] West, 2009[159]	CPAP (20) Sham CPAP (22)	NR	SAQLI, mean (SD) Baseline 4.3 (1.1) 4.4 (0.9) Change from BL at 12 weeks: +0.8 (1.0) +0.03 (1.2) Between-group diff (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
Wimms, 2020[195] MERGE	Total (233) CPAP (115) Standard care (118)	NR	Very mild OSA SF-36 MCS Within-group diff (95% CI) 5.8 (3.6 to 8.1) -0.8 (-3.2 to 1.6) Between-group diff (95% CI) 6.6 (3.3 to 9.9), p=0.0001 SF-36 PCS (mean, SD) SF-36 PCS Within-group mean change (95% CI) 0.8 (-0.9 to 2.5) -2.1 (-3.9 to -0.3)	NR	NR	NR	CPAP: 1 (0.8) Standard care: 1 (0.8)	NR	NR

Appendix E Table 4. 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 (%)
Wimms, 2020[195] MERGE (continued)			Between-group diff (95% CI) 2.9 (0.4 to 5.4), p=0.03 Mild OSA SF-36 MCS (mean, SD) BL 46.9 (11.1) 44.3 (12.3) Within-group diff (95% CI) 4.2 (2.8 to 5.6) -0.7 (-2.1 to 0.7) Between-group diff (95% CI) 4.9 (2.9 to 6.9), p<0.0001 SF-36 PCS (mean, SD) BL: 48 (9.7) 47.2 (10.2) Within-group diff (95% CI) 1 (-0.1 to 2.2) -0.7 (-1.8 to 0.4) Between-group diff (95% CI) 1.7 (0.1 to 3.3), p=0.05						

Appendix E Table 4. 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 (%)
Wimms, 2020[195] MERGE (continued)			FOSQ, mean (SD) BL: 16.4 (2.9) 15.9 (2.7) 12 weeks 18 (NR) 16.1 (NR) Within-group diff (95% CI) 1.6 (1.1 to 2.0) 0.2 (-0.2 to 0.7) Between-group diff (95% CI) 1.3 (0.7 to 2), p<0.0001 EQ-5D: Index, mean (SD) BL: 0.76 (0.19) 0.74 (0.19) Change at 12 weeks (95% CI) 0.03 (0 to 0.06) 0 (-0.03 to 0.02) Between-group diff (95% CI) 0.03 (0 to 0.07), p=0.08 EQ-5D: VAS, mean (SD) BL: 70.9 (18.8) 65.8 (18.5)						

Appendix E Table 4. 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 (%)
Wimms, 2020[195] MERGE (continued)			Change at 12 weeks (95% CI) 3.1 (0.3 to 5.9) -0.9 (-3.7 to 1.8) Between-group diff (95% CI) 4 (0.1 to 7.9), p=0.05						
Zhao, 2017[196] BestAIR	Total (169) CPAP (83) Control+ Sham (86)	NR	SF-36 PCS, mean (SD) BL: 45.2 (9.4) 44.3 (9.6) 12 weeks 45.6 (9.7) 42.7 (10.1) 24 weeks 46.2 (9.6) 42.9 (8.7) Between-group diff (95% CI) 3.4 (1.4 to 5.3), p<0.001 SF-36 MCS BL: 49.7 (12) 50.3 (0.6) 12 weeks 52.2 (11.3) 52.2 (9.7) 24 weeks 51.3 (9.7) 54 (11.5) Between-group diff (95% CI) 0.2 (-2.1 to 2.4), p=0.869	NR	NR	NR	Total: 4 (2.4) CPAP: 2 (2.4) Control+Sham: 2 (2.3)	NR	NR

* For all-cause mortality, the authors also reported an incidence density ratio: 2.6 (95% CI, 0.70 to 11.8; p=0.16).
† Hospitalizations were for unstable angina or arrhythmias.
ǂ Authors also reported 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.

Appendix E Table 4. Results of Included Randomized, Controlled Trials Assessing CPAP: Health Outcomes (KQ 5)

[l] 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 processing.
[**] 2 second presentation rate.
[††] Benton visual retention test.
[‡‡] Per authors, one person in the control group developed "unspecified tachyarrhythmia requiring hospitalization."
[§§] Authors reported counts for neurological "adverse events" but did not specify how these were measured or defined: CPAP 36 events (6.5%) vs. sham 32 events (5.9%).
[ll] 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.

Abbreviations: A3=Atrial Fibrillation, Apnea, Airway Pressure; adj=adjusted; A-fib=atrial fibrillation; APPLES=Apnea Positive Pressure Long-term Efficacy Study; BestAIR=Best Apnea Interventions for Research; BL=baseline; BSC=best supportive care; BVRT=Benton Visual Retention Test; CATNAP=CPAP Apnea Trial North American Program; CBV=cerebrovascular; CI=confidence interval; COWAT=Controlled Oral Word Association Test; CPAP=continuous positive airway pressure; CV=cardiovascular; CVD=cardiovascular disease; diff=difference; EQ=EuroQoL; FOSQ=Functional Outcomes of Sleep Questionnaire; G=group; HeartBEAT=Heart Biomarker Evaluation in Apnea Treatment; HF=heart failure; IQ=intelligence quotient; KQ=key question; MCS=Mental Component Score of the SF-36; MI=myocardial infarction; MLHF=Minnesota Living with Heart Failure; MOSAIC=Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular; 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; OSA=obstructive sleep apnea; 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; QSQ=Quebec Sleep Questionnaire; RAVLT=Rey Auditory Verbal Learning Test; RICCADSA=Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA; RVIP=Rapid Visual Information Processing; RVIPT=Rapid Visual Information Processing Test; SAQLI=Sleep Apnea Quality of Life Index; SD=standard deviation; SE=standard error; SEM=subjects with a mean; SF-12=12-Item Short Form Health Survey; SF-36=36-Item Short Form Health Survey; TIA=transient ischemic attack; unadj=unadjusted; WAIS=Wechsler Adult Intelligence Scale; WAIS-R=Wechsler Adult Intelligence Scale-Revised.

Appendix E Table 5. Characteristics of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices (KQs 5 and 6)

First Author, Year Design	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Weeks	Mean (Range) Age	% F	% Race/ Ethnicity	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Benefits Quality
Aarab, 2011[206] Nikolopoulou, 2020[207] Parallel	MAD (20) Intraoral pbo 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[208] Parallel	MAD (36) Intraoral sham/pbo device (36)	Sleep clinics	No	Sweden	12	58	21	NR	29–30	23–24	11	Mild to severe	100; NR	Fair
Barnes, 2004[164] Cross-over	MAD† (99) Pbo (98)	Referrals	No	Australia	12 CPAP; 12 MAD; 12 placebo	47	20	NR	31	21	11	Mild to mod	15; NR	Fair
Bloch, 2000[209] 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[210] 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
Gagnadoux, 2017[216] Parallel	MAD (75) Sham (75)	Sleep centers	No	France	8	54	14	NR	27	41	9	Severe	21; NR	Fair
Johnston, 2002[214] Cross-over	Total (21) MAD first (13) Sham MAD first (8)	Sleep clinic	No	Ireland	4–6 active; 4–6 sham	55	19	NR	32	32	14	Mild to severe	NR; 0	Fair
Lam, 2007[177] Parallel	MAD‡ (34) Usual care§ (33)	Sleep center	No	Hong Kong	10	46	22	NR	27	21	12	Mild to severe‖	19; NR	Fair
Marklund, 2015[217] Parallel	MAD (45) Pbo device (46)	Clinic referrals	No	Sweden	16	52	32	NR	28	16	11	Mild to mod	NR; NR	Fair
Naismith, 2005[211] Gotsopoulos, 2002[212] Gotsopoulos, 2004[213] Cross-over	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[218] 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 5. Characteristics of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices (KQs 5 and 6)

First Author, Year Design	G1 (N) G2 (N)	Source of Patients	Screen Detected?	Country	Duration, Weeks	Mean (Range) Age	% F	% Race/ Ethnicity	Mean BMI	Mean AHI	Mean ESS	OSA Severity	% HTN; % HF	Benefits Quality
Quinnell, 2014[215] 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	20	NR	31	14	12	Mild to mod	26; NR	Fair

* Study also included a CPAP arm.

[l] Study also included a CPAP arm. Because six different orders were possible, study authors did not list individuals' actual orders. Numbers represent the number of people who started treatment in that arm (104 total participants; 80 completed all three arms).

[ǂ] Study also included a CPAP arm.

[§] Usual care was defined as conservative measures—sleep hygiene and weight loss advice (if applicable).

[l] Authors defined as "mild to moderate," but 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; KQ=key question; MAD=mandibular advancement device; mod=moderate; N=sample size; NR=not reported; OSA=obstructive sleep apnea; pbo=placebo; pts=patients; SP=SleepPro; tx=treatment.

Appendix E Table 6. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)	Other, N (%)
Aarab, 2011[206] Nikolopoulou, 2020[207]	MAD (20) Intraoral pbo 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	Clinical signs of TMD Baseline: 0 (0) 0 (0) 6 months: 0 (0) 0 (0) NS FIRS score (25%|median|75%) Baseline: 0|0|1 0|0|0 6 months 0|0|0.50 0|0|0 NS
Barnes, 2004[164]	MAD (99) Pbo (98)	0 (0.0) 0 (0.0)	NR	Reported: Word Pair Memory Recall; Logical Memory Test; Digit Span Backwards; Trail Making B; Digit Symbol Substitution Task; COWAT; PVT; Stroop Color Association Test	NR	NR	NR	NR	NR	NR

Appendix E Table 6. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)	Other, N (%)
Barnes, 2004[164] (continued)			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. pbo 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. pbo 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. pbo p=NS Sexual relationships: Baseline: 2.9 (0.1) 3.0 (0.1), p=NS 3.0 (0.1), p=NS MAD vs. pbo p=NS Social outcomes: Baseline: 3.3 (0.1) 3.7 (0.1), p<0.001 3.4 (0.1), p=NS MAD vs. pbo 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. pbo 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							

Appendix E Table 6. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)	Other, N (%)
Barnes, 2004[164] (continued)			MAD vs. pbo p=NS Overall health Baseline: 65.9 (1.7) 71.7 (1.6); p<0.001 68.7 (1.6); p=NS MAD vs. pbo p<0.05							
Bloch, 2000[209]	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	NR
Lam, 2007[177]	MAD (34) Usual care (33)	NR	SAQLI, mean (SEM) continued Treatment-related symptoms Mean (SEM) 10 weeks 1.8 (0.2) SF-36, mean (SEM); p-value of within-group change from BL; between-group change from BL vs. usual care Physical function BL 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 BL 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 BL 65.8 (2.9) 65.6 (2.5) Mental health 10 weeks	NR	NR	NR	NR	NR	NR	NR

Appendix E Table 6. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)	Other, N (%)
Lam, 2007[177] (continued)			69.8 (3.1); p=NS; p=NS 68.0 (2.5)							
Marklund, 2015[217]	MAD (45) Pbo device (46)	NR	SF-36 PCS, mean (SD) BL: 45.9 (8.9) 45.3 (8.5) 16 weeks 48.2 (8.4) 46 (10.3) Between-group diff (95% CI) 2.2 (-1.8 to 6.3) SF-36 MCS, mean (SD) BL: 44.3 (10.8) 46.1 (10.5) 16 weeks 48.1 (9.7) 47.2 (12.1) Between-group diff (95% CI) 0.9 (-3.8 to 5.6) FOSQ BL: 16.1 (2.3) 16.3 (2.6) 16 weeks 17.6 (2.3) 16.4 (3.4) Between-group diff (95% CI) 1.2 (-0.1 to 2.5)	NR	NR	NR	NR	NR	BL: NR (84) NR (77) Followup: NR (71) NR (70)	NR
Petri, 2008[218]	MAD (33) Sham MAD (30) No tx (30)	0 (0.0) 0 (0.0) 1 (3.3)	SF-36 PCS, Mean (SD) BL: 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	NR	NR	NR	NR	NR	NR	NR

Appendix E Table 6. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)	Other, N (%)
Petri, 2008[218] (continued)			SF-36 MCS, Mean (SD) BL: 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							
Quinnell, 2014[215]	Total (90) No tx (22) SP1 MAD (23) SP2 MAD (22) bMAD (23)	0 0 0 0	FOSQ (p-value 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 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	NR	2 (3%) 1 (1%) 0 (0%) 2 (3%)	1 (1%) 0 (0%) 0 (0%) 1 (1%)	NR	NR	NR	NR

Appendix E Table 6. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

First Author, Year	G1 (N) G2 (N)	Mortality, N (%)	Quality of Life	Cognitive Impairment	MVAs, N (%)	CV Events, N (%)	CBV Events, N (%)	Heart Failure, N (%)	Headache, N (%)	Other, N (%)
Quinnell, 2014[215] (continued)			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 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; FIRS=Function Impairment Rating Scale; FOSQ=Functional Outcomes of Sleep Questionnaire; G=group; GHP=general health perceptions; HT=health transition; KQ=key question; 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; pbo=placebo; PCS=Physical Component Score of the SF-36; PF=physical functioning; PVT=Psychomotor Vigilance Test; RE=role

Appendix E Table 6. Results of Included Randomized, Controlled Trials That Evaluated Mandibular Advancement Devices: Health Outcomes (KQ 5)

emotional; SAQLI=Sleep Apnea Quality of Life Index; SD=standard deviation; SE=standard error; SEM=subjects with a mean; SF=social functioning; SF-36=36-Item Short Form Health Survey; SP=SleepPro; TMD=temporomandibular disorder; tx=treatment; Vit=vitality.

Appendix E Table 7. Results of Included Randomized, Controlled Trials: Harms of CPAP Compared With Sham or Control (KQ 6)

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[171] Fair	Total (37) CPAP first (NR) Oral pbo 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[137] Fair	CPAP (28) Sham CPAP (28)	0 (0.0) 5 (17.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kushida, 2012[141] Batool-Anwar, 2016[142] 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[177] 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[219] 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[189] 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
Shaw, 2016[193] Fair	CPAP (151), Control (147)	1 (0.6) 1 (0.6)	NR	NR	NR	NR	NR	1 (0.7) 0 (0.0)	1 (0.7) 1 (0.7)	NR	NR
Smith, 2007[156] 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

Appendix E Table 7. Results of Included Randomized, Controlled Trials: Harms of CPAP Compared With Sham or Control (KQ 6)

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 (%)
Weaver, 2012[157] CATNAP Fair	CPAP (141) Sham CPAP (140)	1 (0.8) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Weinstock, 2012[201, 220] 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: APPLES=Apnea Positive Pressure Long-term Efficacy Study; CATNAP=CPAP Apnea Trial North American Program; CPAP=continuous positive airway pressure; DC=discontinued; G=group; KQ=key question; meds=medications; N=sample size; NR=not reported; pbo=placebo; TMJ=temporomandibular.

Appendix E Table 8. Results of Included Randomized, Controlled Trials: Harms of MADs Compared With Sham or Control (KQ 6)

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 (%)	Excess Saliv, N (%)	Pain, N (%)	Dental, N (%)	Other
Aarab, 2011[206] Nikolopoulou, 2020[207] Fair	MAD (20) Intraoral pbo 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[209] Fair	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[210] Fair	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)	
Gagnadoux, 2017[216] Fair	MAD (75) Sham (75)	0 (0.0) 0 (0.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR	Mean side effect score‡ (Range) 2 (1–4) 2 (0–3) p=0.14

Appendix E Table 8. Results of Included Randomized, Controlled Trials: Harms of MADs Compared With Sham or Control (KQ 6)

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 (%)	Excess Saliv, N (%)	Pain, N (%)	Dental, N (%)	Other
Johnston, 2002[214] Fair	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)	
Lam, 2007[177] Fair	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)	
Marklund, 2015[217] Fair	MAD (45) Pbo device (46)	0 (0.0)	NR	NR	NR	NR	NR	NR	N NR, but statistic-ally significant (p=0.03)	N NR, but statistically significant for jaw pain (p=0.004), and tooth pain (p=0.02)	N not reported, but statistically significant for bite changes (p<0.001)	Restless legs (BL, followup) Oral device: (41%, 13%) p<0.001 Pbo: (31%, 31%) Diff: (28%, p=0.02); also reported nasal congestion, fatigue, and nightmares
Naismith, 2005[211] Gotsopoulos, 2002[212] Gotsopoulos, 2004[213] Fair	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[218] Fair	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)	

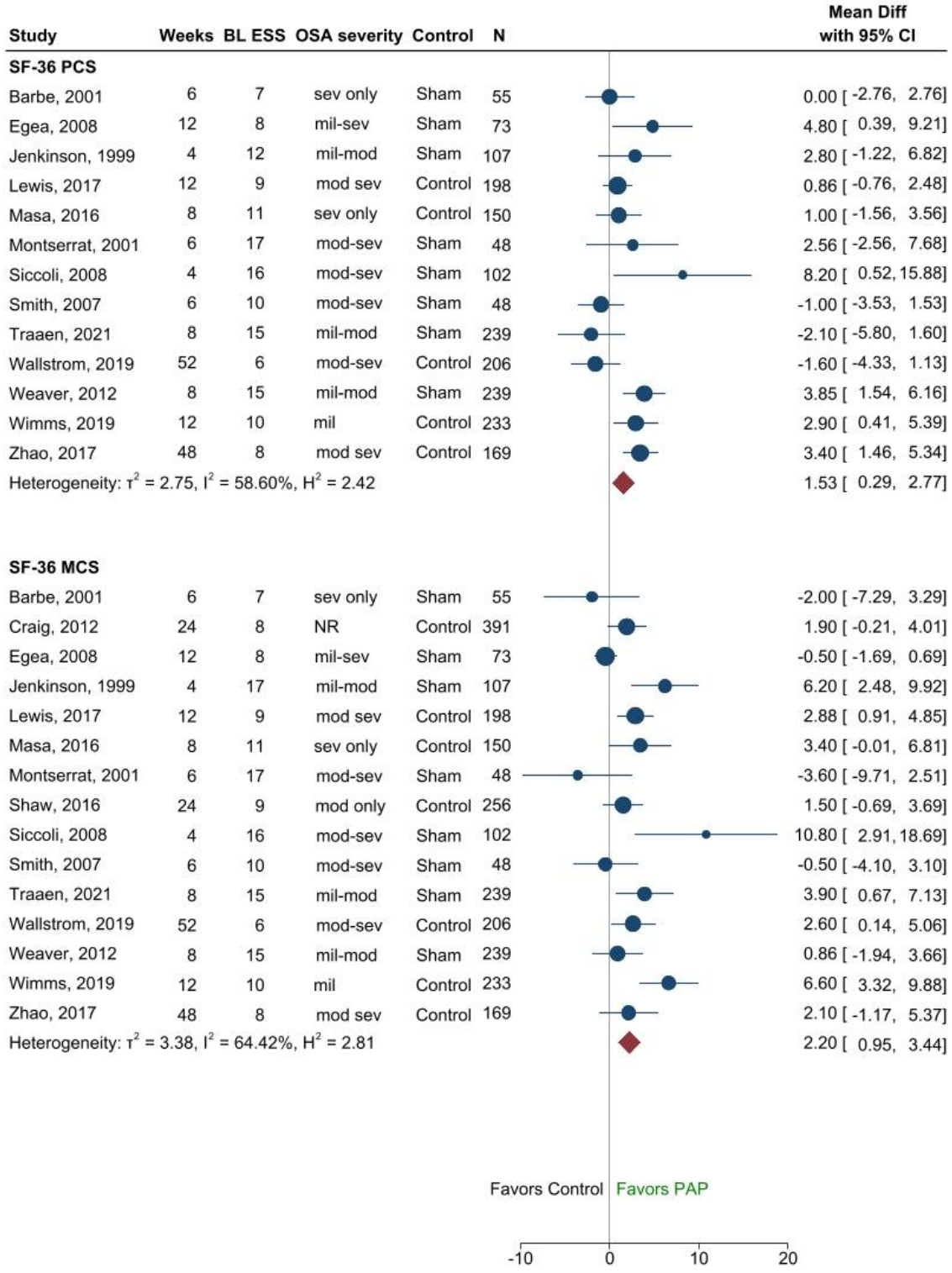
Appendix E Table 8. Results of Included Randomized, Controlled Trials: Harms of MADs Compared With Sham or Control (KQ 6)

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 (%)	Excess Saliv, N (%)	Pain, N (%)	Dental, N (%)	Other
Quinnell, 2014[215] TOMADO Fair	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).
ǂ Participants were asked to rate (0, absent; 1, mild; 2, moderate; 3, severe) six common side effects of oral appliance therapy, including jaw pain, tooth pain, muscle stiffness, dry mouth, hypersalivation, and occlusal change.
§ Data were for "discomfort/mouth problems."

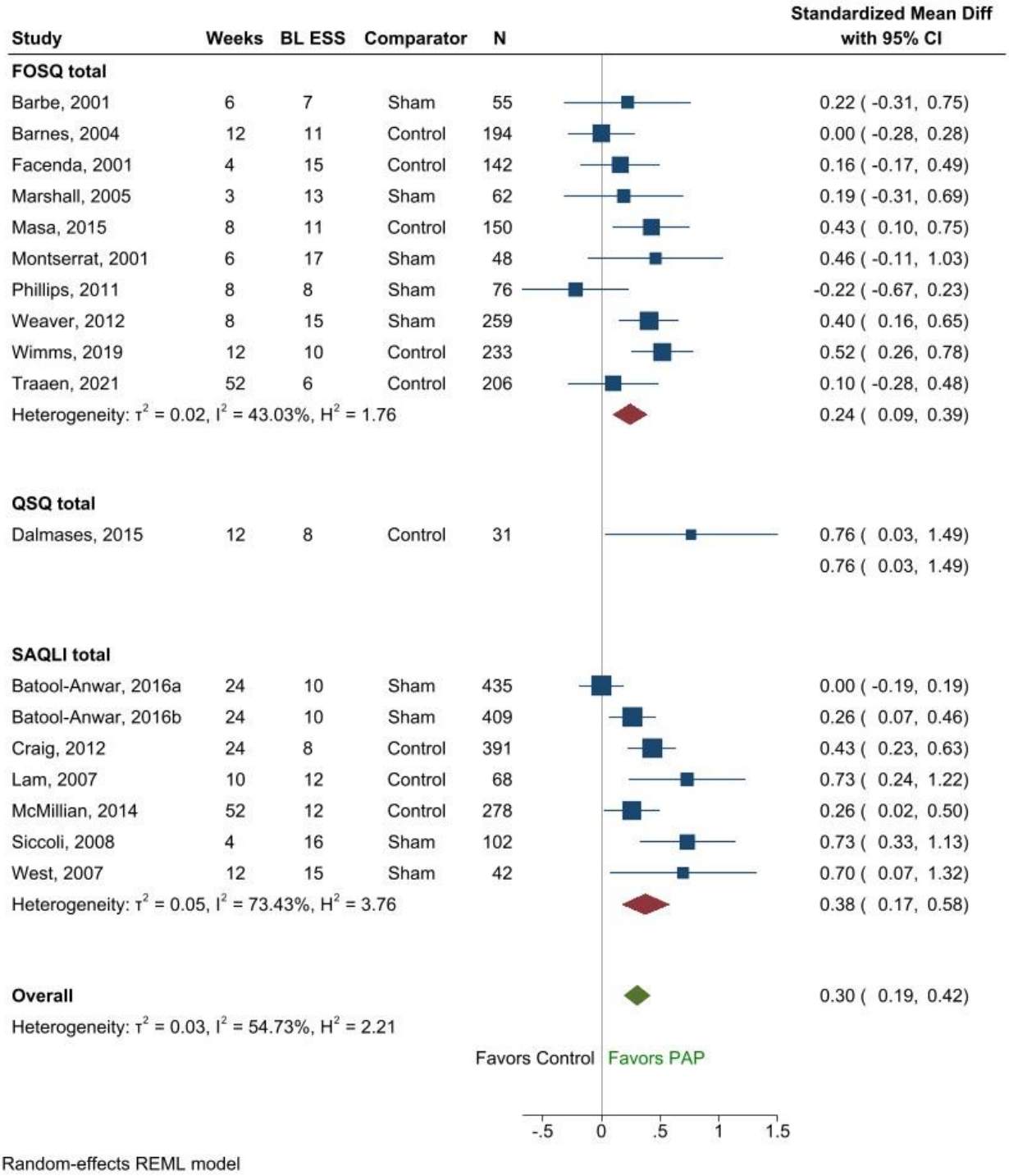
Abbreviations: addl=additional; BL=baseline; bMAD=fully bespoke mandibular advancement device; claustro=claustrophobia; DC=discontinued; diff=difference; G=group; KQ=key question; meds=medications; MAD=mandibular advancement device; N=sample size; NR=not reported; pbo=placebo; saliv=salivation; SP=SleepPro; TMJ=temporomandibular; TOMADO=Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea-hypopnoea; tx=treatment.

Appendix F Figure 1. Comparison of PAP vs. Inactive Control for Change in Short Form (36) Health Survey Mental Component Summary (SF-36 MCS) and Physical Component Summary (SF-36 PCS)



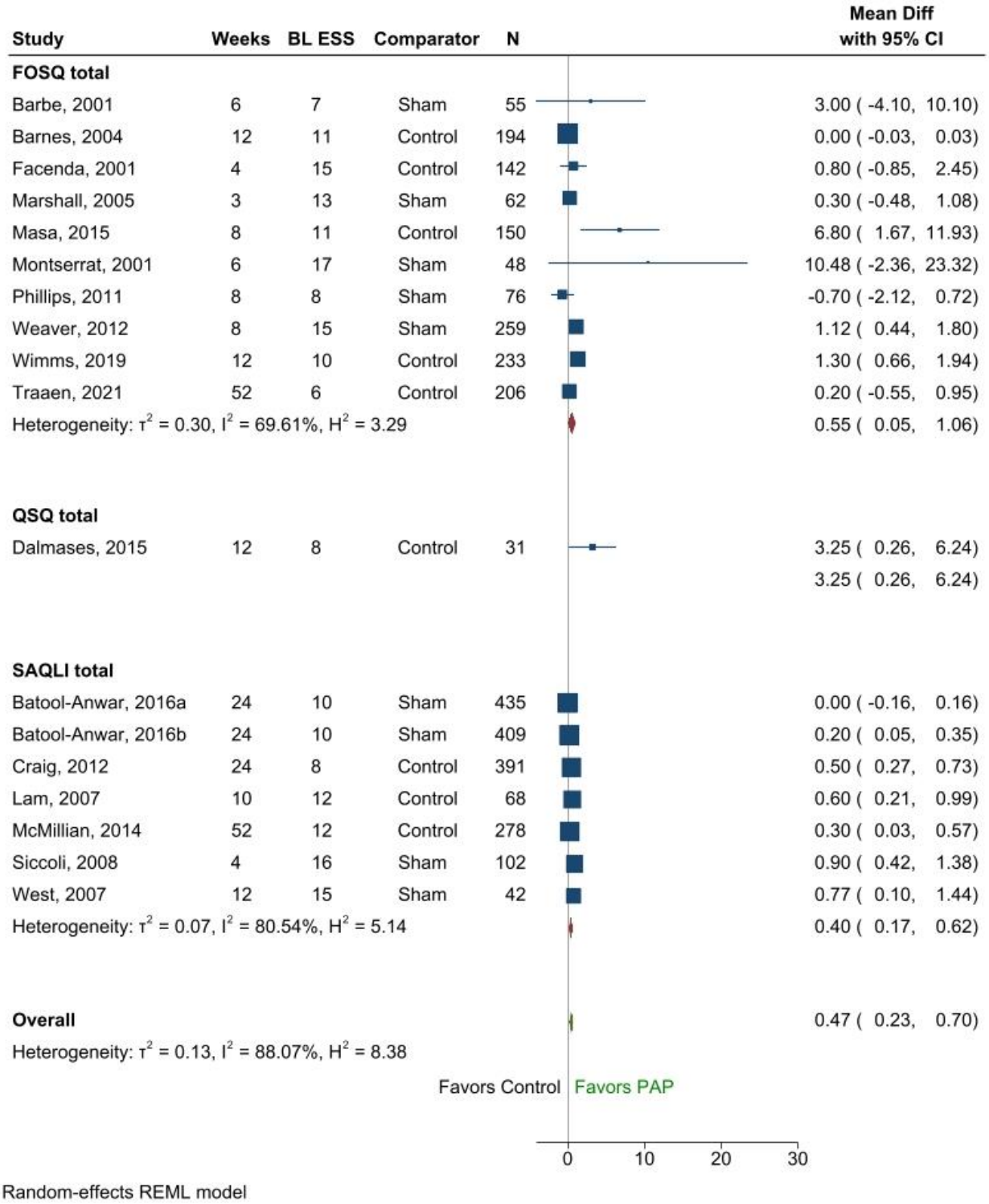
Abbreviations: BL=baseline; CI=confidence interval; Diff=difference; ESS=Epworth Sleepiness Scale; H^2=H^2 statistic; I^2=I^2 statistic; MCS=mental component summary; mil=mild; mod=moderate; N=number; OSA=obstructive sleep apnea; PAP=positive airway pressure; PCS=physical component summary; REML=restricted maximum-likelihood estimation; sev=severe; SF-36=Medical Outcome Short-Form (36-Item) Health Survey; T^2=T^2 statistic; vs.=versus.

Appendix F Figure 2. Comparison of PAP vs. Inactive Control for Change in Sleep-Related Quality of Life, Pooled Standardized Mean Difference



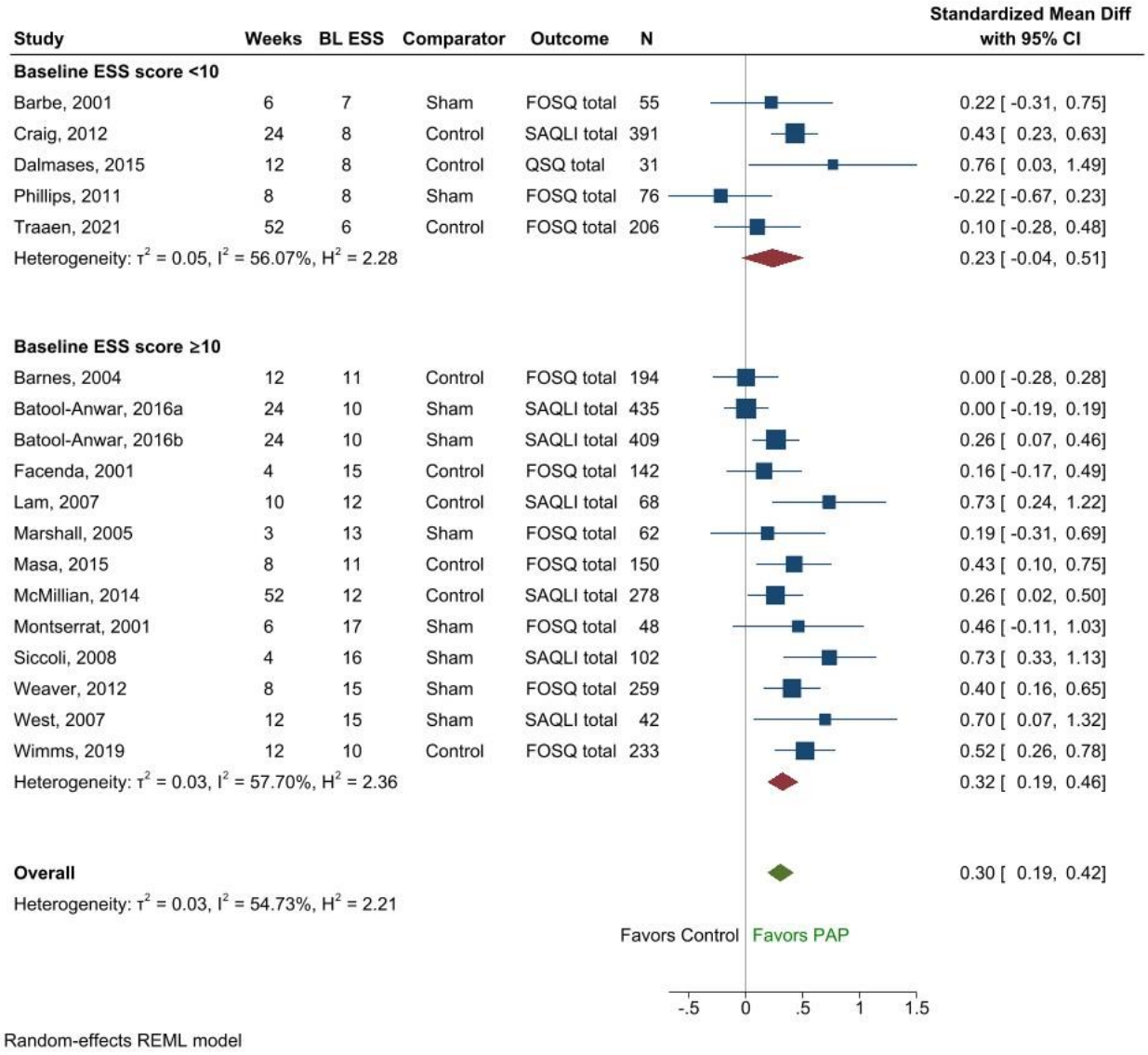
Abbreviations: BL=baseline; CI=confidence interval; Diff=difference; ESS=Epworth Sleepiness Scale; FOSQ=Functional Outcomes of Sleep Questionnaire; H^2=H^2 statistic; I^2=I^2 statistic; N=number; PAP=positive airway pressure; QSQ=Quebec Sleep Questionnaire; REML=restricted maximum-likelihood estimation; SAQLI=Sleep Apnea Quality of Life Index; T^2=T^2 statistic; vs.=versus.

Appendix F Figure 3. Comparison of PAP vs. Inactive Control for Change in Sleep-Related Quality of Life, Difference in Change From Mean Baseline Scores



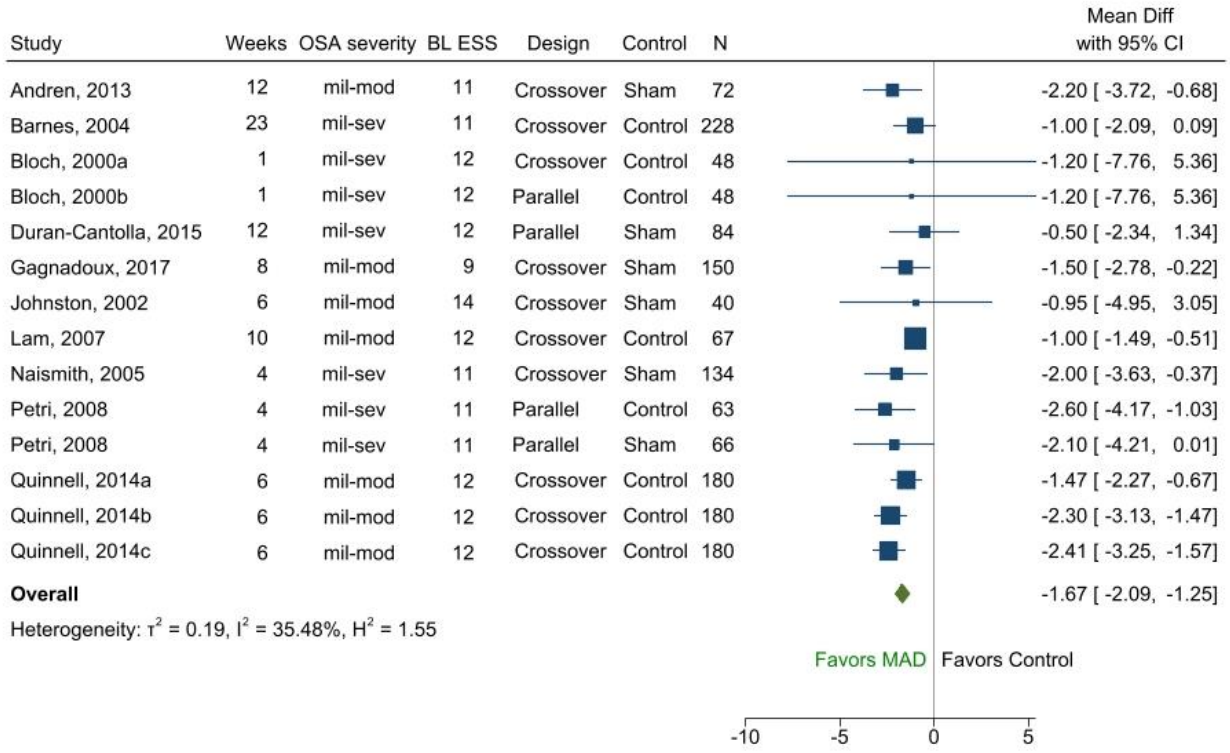
Abbreviations: BL=baseline; CI=confidence interval; Diff=difference; ESS=Epworth Sleepiness Scale; FOSQ=Functional Outcomes of Sleep Questionnaire; H^2=H^2 statistic; I^2=I^2 statistic N=number; PAP=positive airway pressure; QSQ=Quebec Sleep Questionnaire; REML=restricted maximum-likelihood estimation; SAQLI=Sleep Apnea Quality of Life Index; T^2=T^2 statistic; vs.=versus.

Appendix F Figure 4. Comparison of PAP vs. Inactive Control for Change in Sleep-Related Quality of Life, Sensitivity Analysis Limited to Trials With Mean Baseline ESS ≥10



Abbreviations: BL=baseline; CI=confidence interval; Diff=difference; ESS=Epworth Sleepiness Scale; FOSQ=Functional Outcomes of Sleep Questionnaire; H^2=H^2 statistic I^2=I^2 statistic; N=number; PAP=positive airway pressure; QSQ=Quebec Sleep Questionnaire; REML=restricted maximum-likelihood estimation; SAQLI=Sleep Apnea Quality of Life Index; T^2=T^2 statistic; vs.=versus.

Appendix F Figure 5. Comparison of MAD vs. Inactive Control for Change in ESS



Abbreviations: BL=baseline; CI=confidence interval; Diff=difference; ESS=Epworth Sleepiness Scale; FOSQ=Functional Outcomes of Sleep Questionnaire; H^2=H^2 statistic; I^2=I^2 statistic; MAD=mandibular advancement device; mil=mild; mod=moderate; N=number; OSA=obstructive sleep apnea; sev=severe; T^2=T^2 statistic; vs.=versus.