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Screening for Obstructive Sleep Apnea in Adults
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Obstructive sleep apnea (OSA) is associated with adverse health outcomes.

OBJECTIVE To review the evidence on screening for OSA in asymptomatic adults or those with unrecognized OSA symptoms to inform the US Preventive Services Task Force.

DATA SOURCES PubMed/MEDLINE, Cochrane Library, Embase, and trial registries through August 23, 2021; surveillance through September 23, 2022.

STUDY SELECTION English-language studies of screening test accuracy, randomized clinical trials (RCTs) of screening or treatment of OSA reporting health outcomes or harms, and systematic reviews of treatment reporting changes in blood pressure and apnea-hypopnea index (AHI) scores.

DATA EXTRACTION AND SYNTHESIS Dual review of abstracts, full-text articles, and study quality. Meta-analysis of intervention trials.

MAIN OUTCOMES AND MEASURES Test accuracy, excessive daytime sleepiness, sleep-related and general health–related quality of life (QOL), and harms.

RESULTS Eighty-six studies were included (N = 11 051). No study directly compared screening with no screening. Screening accuracy of the Multivariable Apnea Prediction score followed by unattended home sleep testing for detecting severe OSA syndrome (AHI ≥30 and Epworth Sleepiness Scale [ESS] score >10) measured as the area under the curve in 2 studies (n = 702) was 0.80 (95% CI, 0.78 to 0.82) and 0.83 (95% CI, 0.77 to 0.90). Five studies assessing the accuracy of other screening tools were heterogeneous and results were inconsistent. Compared with inactive control, positive airway pressure was associated with a significant improvement in ESS score from baseline (pooled mean difference, −2.33 [95% CI, −2.75 to −1.90]; 47 trials; n = 7024), sleep-related QOL (standardized mean difference, 0.30 [95% CI, 0.19 to 0.42]; 17 trials; n = 3083), and general health–related QOL measured by the 36-Item Short Form Health Survey (SF-36) mental health component summary score change (pooled mean difference, 2.20 [95% CI, 0.95 to 3.44]; 15 trials; n = 2345) and SF-36 physical health component summary score change (pooled mean difference, 1.53 [95% CI, 0.29 to 2.77]; 13 trials; n = 2031). Use of mandibular advancement devices was also associated with a significantly larger ESS score change compared with controls (pooled mean difference, −1.67 [95% CI, 2.09 to −1.25]; 10 trials; n = 1540). Reporting of other health outcomes was sparse; no included trial found significant benefit associated with treatment on mortality, cardiovascular events, or motor vehicle crashes. In 3 systematic reviews, positive airway pressure was significantly associated with reduced blood pressure; however, the difference was relatively small (2-3 mm Hg).

CONCLUSIONS AND RELEVANCE The accuracy and clinical utility of OSA screening tools that could be used in primary care settings were uncertain. Positive airway pressure and mandibular advancement devices reduced ESS score. Trials of positive airway pressure found modest improvement in sleep-related and general health–related QOL but have not established whether treatment reduces mortality or improves most other health outcomes.

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Obstructive sleep apnea (OSA) is a sleep disorder marked by episodes of narrowing and obstruction of the upper airway during sleep, resulting in reduction or cessation in breathing.[1] OSA is defined as more than 5 events per hour of partial (hypopnea) or total (apnea) upper airway obstruction despite efforts to breathe.[2] Apnea is defined as total airway obstruction (>90%) for more than 10 seconds, and hypopnea as a partial airway obstruction (>30%) sufficient to cause at least a 3% reduction in blood oxygen saturation or sleep arousals.[3] The apnea-hypopnea index (AHI) is used to define the severity of OSA: mild (5-15 events per hour), moderate (16-30 events per hour), and severe (>30 events per hour). Standardized prevalence estimates using the 2012 American Academy of Sleep Medicine (AASM) scoring criteria were 33.2% for any OSA (AHI ≥5) and 14.5% for moderate to severe OSA (AHI ≥15).[4] Risk factors for OSA include male sex,[5] postmenopausal status,[6] increasing age (40-70 years),[7,8] and higher body mass index (BMI).[5] A variety of adverse health outcomes are associated with untreated OSA, including cardiovascular disease events, coronary heart disease, heart failure, atrial fibrillation, and stroke. Severe OSA (AHI ≥30) is associated with increased all-cause mortality.[9,10]

In 2017, the US Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for OSA in asymptomatic adults (I statement).[11] This updated review assessed the current evidence on OSA screening in individuals and settings relevant to US primary care and was used to update the USPSTF recommendation.

Methods

Scope of Review

Figure 1 shows the analytic framework and key questions (KQs) that guided the review. Detailed methods are available in the full evidence review.[13] In addition to the KQs, this review looked for evidence related to 2 contextual questions that focused on barriers to undergoing diagnostic testing for OSA and the association between AHI and health outcomes (eContextual Questions in the Supplement).

Data Sources and Searches

PubMed/MEDLINE, the Cochrane Library, and Embase were searched for English-language articles published through August 23, 2021 (eMethods in the Supplement). ClinicalTrials.gov was searched for unpublished studies. The searches were supplemented by reviewing reference lists of pertinent articles, studies suggested by peer reviewers, and comments received during public commenting periods. From August 23, 2021, through September 23, 2022, 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.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using prespecified eligibility criteria (eTable 1 in the Supplement). Disagreements were resolved by consensus. For all KQs, English-language studies of adults 18 years or older conducted in countries categorized as "very high" on the Human Development Index[14] and rated as fair or good quality were included.

For KQ1 and KQ3 (direct evidence of benefits and harms of screening) and KQ2 (accuracy of screening tools), studies of asymptomatic adults with OSA or persons with unrecognized OSA symptoms were included. For KQ1 and KQ3, randomized clinical trials (RCTs) comparing screened groups with nonscreened groups and reporting on health outcomes were eligible. For KQ2, prospective cohort studies and cross-sectional studies assessing the accuracy of screening questionnaires or clinical prediction tools (alone or followed by an unattended home sleep test) compared with polysomnography conducted in a sleep laboratory were eligible. For KQ2, studies limited to persons referred to sleep laboratories for suspected OSA were excluded. For KQ3 (harms of screening), studies eligible for KQ1 or KQ2 that reported harms of screening or diagnostic tests (eg, false-positive results leading to unnecessary treatment, anxiety, distress, or stigma) were eligible.

For KQs 4 through 6 (benefits and harms of treatment), studies were limited to those of interventions considered first-line treatment for persons diagnosed with OSA (positive airway pressure or mandibular advancement devices [MADs]) compared with inactive control; other interventions (eg, weight loss interventions, oral surgical procedures) were excluded. For KQ4 (benefit of treatment for improving intermediate outcomes), good-quality, recent (within 5 years) systematic reviews comparing positive airway pressure or MADs with an inactive control and reporting on changes in blood pressure or AHI were included. For KQs on the benefits of treatment for improving health outcomes (KQ5) and on the harms of treatment (KQ6), RCTs of adults with a confirmed diagnosis of OSA were eligible.

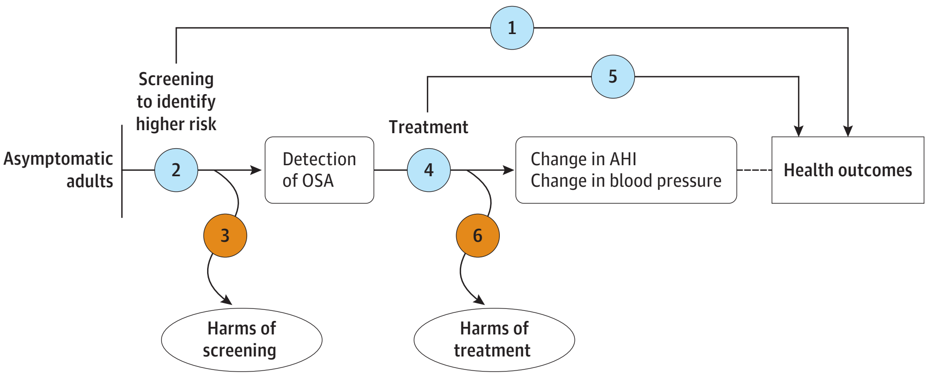
Data Extraction and Quality Assessment

For each study, 1 investigator extracted information about populations, tests or interventions, comparators, outcomes, settings, and designs, and a second investigator reviewed the information for completeness and accuracy. Two investigators independently assessed the quality of included studies using criteria defined by the USPSTF adapted for this topic supplemented with criteria from the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2)[15] and from A Measurement Tool to Assess Systematic Reviews (AMSTAR)[16] (eTables 2-8 in the Supplement). Each study was assigned a final quality rating of good, fair, or poor; disagreements were resolved by discussion and consensus.

Data Synthesis and Analysis

Findings for each KQ were summarized in tables, figures, and narrative format. To determine whether meta-analyses were appropriate, the clinical and methodological heterogeneity of the studies were assessed following established guidance.[17] For KQ5, random-effects restricted maximum likelihood models were conducted on continuous measures of sleepiness, general health–related quality of life (QOL), and sleep-related QOL associated with positive airway pressure and MAD use when at least 3 similar studies were available, analyzing the mean difference in change from the baseline score or the standardized mean difference (SMD). The *meta* command in Stata version 16 was used to conduct all quantitative analyses.[18] The I^2 statistic was used to assess the statistical heterogeneity in effects between studies.[19-21] Statistical significance was assumed when 95% CIs of pooled results did not cross the null. All testing was 2-sided.

Figure 1. Analytic Framework and Key Questions: Screening for Obstructive Sleep Apnea in Adults



Key questions

1. Does screening for 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 (eg, 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. Are there harms associated with screening or subsequent diagnostic testing for OSA, including for specific subgroups of interest?
4. How effective is treatment with PAP or MADs for improving intermediate outcomes (ie, the 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. Are there harms associated with treatment of OSA using PAP or MADs, including for specific subgroups of interest?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line depicts a health outcome that follows an intermediate outcome. For additional information, see the USPSTF Procedure Manual.[12] AHI indicates apnea/hypopnea index; MAD, mandibular advancement device; OSA, obstructive sleep apnea; PAP, positive airway pressure.

Results

A total of 86 studies (reported in 101 articles; N = 11 051) were included (**Figure 2**) in the review. Individual study quality ratings are reported in eTables 2 through 8 in the Supplement.

Benefits of Screening

Key Question 1. Does screening for OSA in adults improve health outcomes, including for specific subgroups of interest?

No eligible studies addressed this question.

Accuracy of Screening

Key Question 2. What is the accuracy of screening questionnaires, clinical prediction tools, and multistep screening approaches (eg, 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?

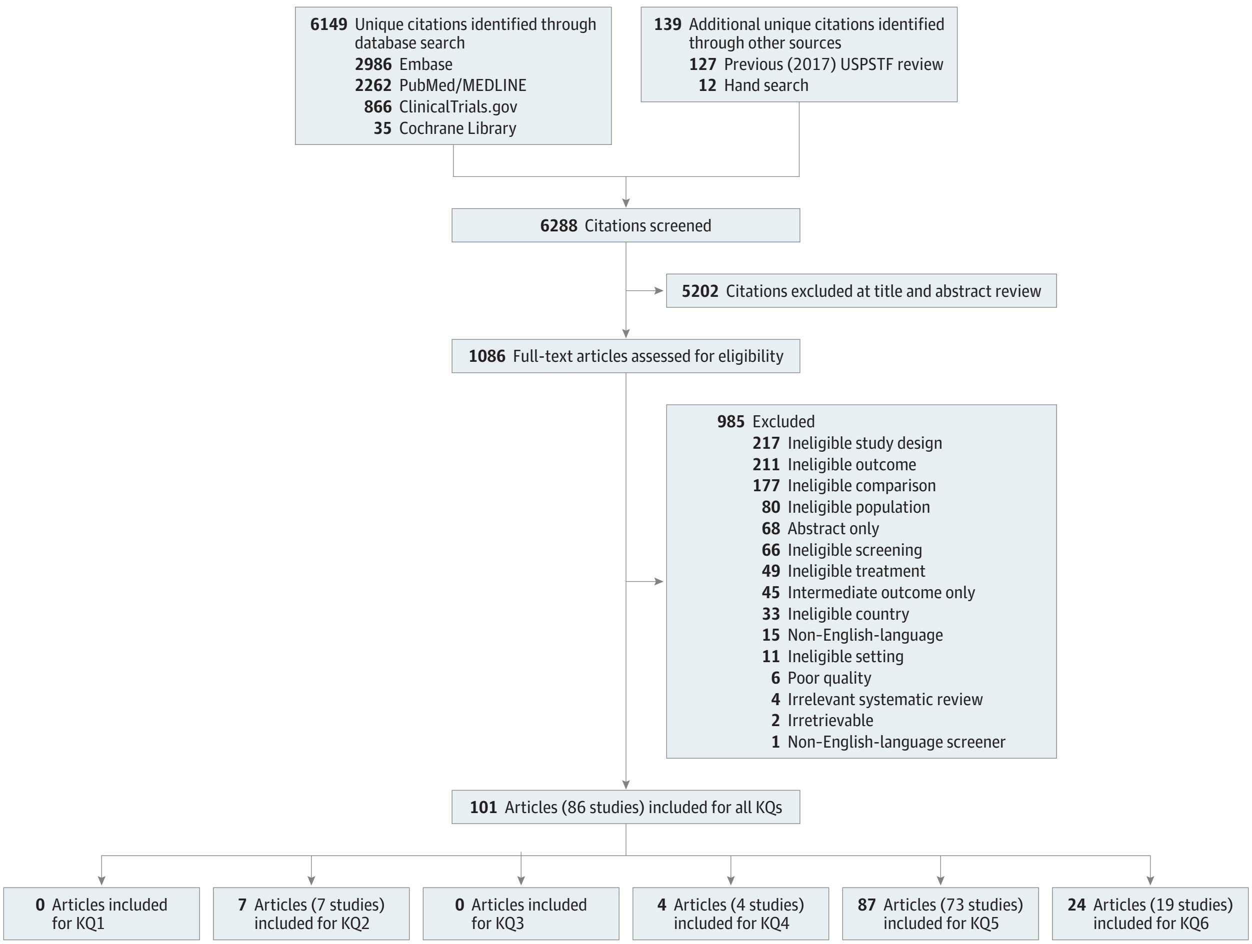
Seven fair-quality studies (n = 2589)[22-28] assessing clinical prediction tools or screening questionnaires compared with facility-based polysomnography were included, 4 of which were new to this review (**Table 1**).[25-28] Two evaluated the Berlin Questionnaire,[22,25] 4 evaluated the STOP-BANG (snoring, tiredness, observed apnea, high blood pressure, BMI, age, neck circumference, gender) questionnaire,[25-28] and 2 evaluated the Multivariable Apnea Prediction (MVAP) score—alone and when followed by an unattended home sleep test.[23,24]

Berlin Questionnaire

The Berlin Questionnaire includes 10 questions about snoring, tiredness, and blood pressure and gathers information on age, sex, height, and weight to classify OSA risk.[29] Two included studies of the Berlin Questionnaire enrolled different populations. One sampled Norwegians from the National Population Register.[22] Of those who responded, 24% were classified as high risk on the Berlin Questionnaire. The final sample enrolled a population with a mean age of 48 years, 45% were women, the mean BMI was 28 (calculated as weight in kilograms divided by height in meters squared), and the median AHI was 6.4. Although the group receiving polysomnography 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 assessing the Berlin Questionnaire[25] included a small (n = 43) but unselected sample of adults with type 2 diabetes recruited from a US general internal medicine clinic. A majority (53%) were female, the mean BMI was 38.3, and the mean AHI was 31.2.

The study enrolling Norwegian participants[22] found suboptimal screening accuracy for AHI 5 or greater (sensitivity, 37%; specificity, 84%) and for AHI 15 or greater (sensitivity, 43%; specificity,

Figure 2. Literature Search Flow Diagram: Screening for Obstructive Sleep Apnea in Adults



The sum of the number of studies per key question (KQ) exceeds the total number of studies because some studies were applicable to multiple KQs. USPSTF indicates US Preventive Services Task Force.

80%) (**Table 2**). The study enrolling US participants with type 2 diabetes from a general internal medicine clinic assessed accuracy for mild (AHI 5-14), moderate (AHI 15-29), and severe (AHI ≥30) OSA.[25] Specificity of the Berlin Questionnaire was suboptimal for all categories of OSA severity (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%).

STOP-BANG Questionnaire

The STOP-BANG questionnaire includes 8 dichotomous items (snoring, tiredness, observed apnea, blood pressure, BMI, age, neck circumference, and gender).[30,31] The 4 studies assessing the accuracy of the STOP-BANG questionnaire enrolled diverse populations and used different scoring criteria and additional variables to determine a positive screen result.[25-28] Detailed characteristics of each study are reported in Table 1.

The heterogeneity of studies and scoring approaches limits the ability to assess consistency of results. Overall, estimates varied, and no study found both high sensitivity and high specificity (Table 2). One study enrolling US adults with type 2 diabetes found good sensitivity for detecting mild (87%), moderate (93%), and severe (94%) OSA but very low specificity for the same subgroups (mild, 0%; moderate, 19%; severe, 15%).[25] In contrast, the study enrolling Spanish adults with Alzheimer disease found modest sensitivity (61%) and somewhat better specificity (76%) for severe OSA.[26] The study of Korean adults found moderate sensitivity (62%) and specificity (64%) for detecting mild through severe OSA.[27] The study of adults receiving opioids for chronic pain provided accuracy data for the STOP-BANG questionnaire alone as well as for the STOP-BANG questionnaire plus resting daytime Spo_2 (first stage). Results for various cutoffs are reported in Table 2; across all screening approaches, sensitivity for the STOP-BANG to detect moderate to severe OSA was very good, but specificity was limited.

MVAP Score

The MVAP score combines symptoms of snoring, choking, and witnessed apnea events with BMI, age, and sex.[32] It rates apnea risk between 0 and 1, with 0 representing the lowest risk and 1 representing the highest risk. The 2 included studies assessing the MVAP were conducted by the same research group from Philadelphia.[23,24] One study evaluated Medicare recipients (n = 452) from the city's greater metropolitan area, most of whom (74%) had daytime sleepiness.[23]

Table 1. Characteristics of Included Studies Assessing the Accuracy of Clinical Prediction Tools or Screening Questionnaires (KQ2)

Source, country	Study design (quality)	Participants	Name of questionnaire(s)/ tool(s)	Age, mean (SD), y	Women, %	Race and ethnicity, %	BMI, mean (SD)	AHI, mean (SD)	Hypertension, %	OSA, %
Hrubos-Strøm et al,[22] 2011 Norway	Cross-sectional (fair)	Participants (n = 518) randomly drawn from Norwegian National Population Register[a]	Berlin Questionnaire (Norwegian translation)	48 (11.2)	45	NR	28 (4.8)	Median, 6.4 (NR)[b]	27	NR
Morales et al,[23] 2012 US	Cross-sectional (fair)	Medicare recipients (n = 452) from greater Philadelphia metro region, most with some daytime sleepiness[c]	MVAP score; MVAP score + AHI from unattended HST	71 (5.4)	70	Black, 61 Caucasian, 36[d]	30 (6.2)	NR	NR	Any OSA, NR Any OSAS (AHI ≥5 and ESS >10), 27[e]
Gurubhagavatula et al,[24] 2013 US	Cross-sectional (fair)	US adults (n = 250) with hypertension from internal medicine practices and a hypertension clinic[f]	MVAP score; MVAP score + AHI from unattended HST	53 (7.7)	20	Black, 59 Caucasian, 40[d]	32 (7.4)	22.5 (22.9)	100	Of the 79% who had in-laboratory polysomnography: Any OSA, 80[g] OSAS, 25[h]
Edmonds et al,[25] 2019 US	Cross-sectional (fair)	US adults (n = 43) with type 2 diabetes from a general internal medicine clinic	STOP-BANG, Berline Questionnaire	NR	53	NR	38 (7.7)	31.2 (28.1)	NR	Mild (AHI 5-14), 28 Moderate (AHI 15-29), 26 Severe (AHI ≥30), 37
Jorge et al,[26] 2019 Spain	Cross-sectional (fair)	Spanish adults (n = 91) with a recent diagnosis of mild to moderate Alzheimer disease	Modified STOP-BANG[i]	Median, 76 (IQR, 73-80)	64	NR	Median, 28 (IQR, 25.2-30.2)	20.7 (10.6-40.3)	57	Mild (AHI 5-14), 26.4 Moderate (AHI 15-30), 25.3 Severe (AHI >30), 37.4
Shin and Baik,[27] 2021	Cross-sectional (fair)	Korean adults (n=1033) enrolled in a population-based cohort study[j]	Modified STOP-BANG[k]	59 (7.9)	48	Asian, 100	25 (3.0)	7.3 (8.9)	38	Mild (AHI 5-14), 32.4 Moderate (AHI 15-29),10.1 Severe (AHI ≥30), 3.1
Selvanathan et al,[28] 2021[l]	Cross-sectional (fair)	Adults (n = 202 and 199[m]) receiving opioids for chronic pain	STOP-BANG; STOP-BANG + resting daytime Spo_2	53 (12.8)	58	NR	29 (6.4)	Median, 6.5 (IQR, 2.3-19.4)	33	NR

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; HST, home sleep test; KQ, key question; MVAP, Multivariable Apnea Prediction; NR, not reported; OSA, obstructive sleep apnea; OSAS, obstructive sleep apnea syndrome; Spo_2, oxygen saturation by pulse oximetry; STOP-BANG, snoring, tiredness, observed apnea, blood pressure, body mass index, age, neck circumference, gender.

[a] Data in this row describe the 518 participants who underwent polysomnography. The 518 were a subset of the larger study population of 16 302 who completed the Berlin Questionnaire. The mean age of the larger study population was 48 years, 53% were women, the mean BMI was 26 (SD, 4.3), and 14% had hypertension.

[b] Standard deviation was not reported, but 25th and 75th percentiles were 1.7 and 18.3, respectively.

[c] Seventy-four percent met their definition of daytime sleepiness (frequency of sleepiness, based on whether they had a problem staying awake, every day or several [≥3] days per week); 32% had ESS scores greater than 10 (Indira Gurubhagavatula, MD, MPH, University of Pennsylvania, email, July 2015).

[d] Caucasian is the term used in the publication.

[e] Mild (AHI 5-15 and ESS >10), 9%; at least moderate (AHI ≥15 and ESS >10), 17%; moderate (AHI 15-30 and ESS >10), 8%; severe (AHI >30 and ESS >10), 8%.

[f] Required to have blood pressure 140/90 mm Hg or greater or to be taking antihypertensive medications.

[g] Mild, 34%; moderate, 22%; severe, 25%.

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

[i] Modified STOP-BANG (age >70 years, BMI >26; neck circumference >26.5 cm).

[j] Validation sample only.

[k] Modified STOP-BANG (age 5-64 years 1 point, 65 years or older 2 points; and waist circumference >85, snoring, observed apnea; high blood pressure, BMI >25; each 1 point).

[l] Although this is a 2-stage study, only the findings from the first stage in which all patients were included are reported.

[m] The n of 202 represents those who received the STOP-BANG and polysomnography; the n of 199 includes those who received STOP-BANG, polysomnography, and resting daytime Spo_2.

Table 2. Results of Included Studies Assessing the Accuracy of Clinical Prediction Tools or Screening Questionnaires (KQ2)

Source	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-Strøm et al,[22] 2011	Berlin Questionnaire, ≥2 positive categories	AHI ≥5[a]	37.2 (36.0-38.4)	84.0 (83.2-84.7)	NR	NR	PPV, 61.3 (59.7-62.9) NPV, 66.2 (65.3-67.1) PLR, 2.3 (2.2-2.5) NLR, 0.8 (0.7-0.8)
		AHI ≥15[a]	43.0 (41.2-44.8)	79.7 (79.0-80.5)	NR	NR	PPV, 33.5 (32.0-35.0) NPV, 85.5 (84.8-86.1) PLR, 2.1 (2.0-2.3) NLR, 0.7 (0.7-0.7)
Morales et al,[23] 2012	MVAP, 0.49	Severe OSAS (AHI ≥30 and ESS >10)	90.0 (NR)	64.4 (NR)	0.78 (0.71-0.85)	NR	NLR, 0.141 (NR) NPTP, 1.1 (NR)
	MVAP + HST[b], uAHI 15	Severe OSAS (AHI ≥30 and ESS >10)	90.9 (NR)	75.7 (NR)	0.83 (0.77-0.90)	NR	NLR, 0.120 (NR) NPTP, 0.01 (NR)
Gurubhagavatula et al,[24] 2013	MVAP, 0.483	Severe OSAS (AHI ≥30 and ESS >10)	91.5 (NR)	43.9 (NR)	0.68 (0.67-0.70)	NR	NLR, 19.0 (NR) NPTP, 0.015 (NR)
	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, 14.8 (NR)
	MVAP + HST, uAHI 18[b]	Severe OSAS (AHI ≥30 and ESS >10)	88.2 (NR)	71.6 (NR)	0.80 (0.78-0.82)	NR	NLR, 0.162 (NR) NPTP, 0.015 (NR)
	MVAP + HST, uAHI 13.5[b]	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 et al,[25] 2019	STOP-BANG ≥3	Mild (AHI 5-14)	87.2 (NR)	0	NR	NR	PPV, 89.5 (NR) NPV, 0 (NR)
		Moderate (AHI 15-29)	92.6 (NR)	18.8 (NR)	NR	NR	PPV, 65.8 (NR) NPV, 60.0 (NR)
		Severe (AHI ≥30)	93.8 (NR)	14.8 (NR)	NR	NR	PPV, 39.5 (NR) NPV, 80.0 (NR)
	Berlin Questionnaire, ≥2 positive categories	Mild (AHI 5-14)	79.5 (NR)	0 (NR)	NR	NR	PPV, 88.6 (NR) NPV, 0 (NR)
		Moderate (AHI 15-29)	88.9 (NR)	31.3 (NR)	NR	NR	PPV, 68.6 (NR) NPV, 62.5 (NR)
		Severe (AHI ≥30)	93.8 (NR)	25.9 (NR)	NR	NR	PPV, 42.9 (NR) NPV, 87.5 (NR)
Jorge et al,[26] 2019	Modified STOP-BANG (age older than 70 y; BMI >26; neck circumference >26.5 cm) ≥2 positive categories	Severe (AHI >30)	61.0 (47-74)	76.0 (59-89)	0.72 (0.61-0.83)	NR	PPV, 81.0 (66-91) NPV, 54.0 (39-69)

(continued)

Table 2. Results of Included Studies Assessing the Accuracy of Clinical Prediction Tools or Screening Questionnaires (KQ2) (continued)

Source	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)
Shin and Baik,[27] 2021	Modified STOP-BANG ≥3 (snoring; observed apnea; high blood pressure; BMI >25; age 5-64 y, 1 point; ≥65 y, 2 points; waist circumference >85 cm; diabetes; male)	All (AHI ≥5)	62.3 (60.5-64.2)	64.5 (62.9-66)	0.73 (0.70-0.76)	NR	PPV, 64 (63.4-64.4) NPV, 71.8 (71.1-72.5)
		Mild to moderate (5 < AHI < 30)	62.0 (60.1-63.9)	63.8 (62.2-65.4)	0.72 (0.69-0.75)	NR	PPV, 61.6 (61.0-62.3) NPV, 72.6 (71.9-73.3)
		Severe (AHI ≥30)	79.1 (77.3-80.9)	53.3 (51.6-54.9)	0.78 (0.72-0.84)	NR	PPV, 6.03 (6.89-6.17) NPV, 99.2 (99.1-99.2)
Selvanathan et al,[28] 2021	STOP-BANG ≥3[c]	Moderate to severe (AHI ≥15)	89.2 (80.1-95.0)	38.0 (33.6-40.7)	NR	NR	NR
	STOP-BANG ≥3 or resting daytime Spo_2 ≤95%[c]	All (AHI ≥5)	92.9 (87.8-96.0)	31.6 (24.5-37.0)	NR	NR	PPV, 67.3 (63.9-69.8) NPV, 73.5 (57.0-86.0) PLR, 1.4 (1.2-1.5) NLR, 0.2 (0.1-0.5)
		Moderate to severe (AHI ≥15)	95.4 (87.7-98.8)	23.1 (19.4-24.8)	NR	NR	PPV, 37.6 (34.6-38.9) NPV, 91.2 (76.5-97.7) PLR, 1.24 (1.0-1.3) NLR, 0.2 (0.05-0.6)
		Severe (AHI ≥30)	100.0 (89.4-100)	21.0 (18.6-21.0)	NR	NR	PPV, 22.4 (20.0-22.4) NPV, 100 (88.4-100) PLR, 1.3 (1.1-1.3) NLR, ∞

Abbreviations: AHI, apnea-hypopnea index; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; ESS, Epworth Sleepiness Scale; HST, home sleep test; KQ, key question; MVAP, Multivariable Apnea Prediction; NLR, negative likelihood ratio; NPTP, negative posttest 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; Spo_2, oxygen saturation by pulse oximetry; STOP-BANG, snoring, tiredness, observed apnea, blood pressure, body mass index, age, neck circumference, gender; uAHI, unattended AHI from home sleep test.

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

[b] Two-stage process using MVAP for everyone, then an unattended HST to estimate AHI for those with an intermediate MVAP score.

[c] Although this is a 2-stage study, only the findings from the first stage in which all patients were included are reported.

The percentage with OSA was not reported, but 27% had OSA syndrome (OSAS) defined as AHI 5 or greater and Epworth Sleepiness Scale [ESS] score greater than 10. The second study evaluated patients with hypertension from internal medicine practices at a Veterans Affairs medical center and a university-based hypertension clinic (n = 250).[24] Eighty percent of participants had OSA (AHI ≥5); of those, 22% had moderate OSA and 25% had severe OSA. Twenty-five percent of all participants had OSAS. The mean ages of participants were 71 years[23] and 53 years,[24] 60% to 64% were non-White, and the mean BMIs were 30 to 32. The study of Medicare recipients included 70% women[23]; the other study included 20% women.[24] Key quality limitations included concern for attrition bias[24] and moderate concern for selection bias or spectrum bias (with high prevalence of OSA, OSAS, and/or sleepiness among those receiving polysomnography) (eTables 2 and 3 in the Supplement).[23,24]

Both studies reported operating characteristics of MVAP to predict severe OSAS (AHI ≥30 and ESS score >10) using MVAP cutoff scores of 0.48 to 0.49 (Table 2). Sensitivity was 90%[23] and 92%,[24] with specificity of 64% and 44%, respectively (95% CIs not reported). The study of Medicare recipients reported reasonable discrimination (area under the curve [AUC], 0.78 [95% CI, 0.71-0.85]), whereas the other study found inadequate discrimination (AUC, 0.68 [95% CI, 0.67-0.70]). An AUC less than 0.70 is thought to indicate inadequate discrimination.[33,34] Calibration, which is often assessed by plotting the predicted risk vs the observed rate,[33] was not reported.

The study of patients with hypertension[24] also reported operating characteristics of MVAP to predict any OSAS (AHI ≥5 and ESS score >10) using an MVAP cutoff score of 0.559. That study reported a sensitivity of 69.4%, a specificity of 56.5%, and an AUC of 0.61.

MVAP Score Followed by Home Sleep Test

The same 2 studies described in the previous section also reported measures of discrimination for the MVAP score followed by an unattended home sleep test compared with in-laboratory polysomnography (Table 1).[23,24] Both reported characteristics to predict severe OSAS (AHI ≥30 and ESS score >10) using different home sleep test AHI cutoffs: 1 used 15,[23] and the other used 18.[24] Both studies found better operating characteristics with MVAP followed by a home sleep test than with MVAP alone (sensitivity, 88%-91%; specificity, 72%-76%; AUC, 0.80-0.83).

The study of patients with hypertension also reported operating characteristics of MVAP to predict any OSAS (AHI ≥5 and ESS score >10) using a home sleep test AHI cutoff of 13.5. It reported a sensitivity of 81%, a specificity of 54%, and an AUC of 0.67.

Harms of Screening

Key Question 3. What are the harms associated with screening or subsequent diagnostic testing for OSA, including for specific subgroups of interest?

No eligible study addressed this question.

Benefits of Treatment

Key Question 4. How effective is treatment with positive airway pressure or MADs for improving intermediate outcomes (ie, the AHI or blood pressure) in persons with OSA, including for specific subgroups of interest?

Four systematic reviews comparing positive airway pressure or MADs with inactive control for reducing AHI or blood pressure were included (eTable 9 in the Supplement).[35-38] For blood pressure outcomes, 1 review of MADs found benefit associated with treatment compared with inactive control (by 1-2 mm Hg); however, differences between groups were imprecise and not statistically significant (eTable 9 in the Supplement).[35] For positive airway pressure, pooled estimates from 1 review found benefit associated with positive airway pressure compared with control for reducing mean 24-hour blood pressure (−2.63 mm Hg [95% CI, −3.86 to −1.39]; 8 trials; n = 994); pooled results for measures of daytime systolic blood pressure and diastolic blood pressure were also significantly lower with positive airway pressure vs control, ranging from −2.76 to −1.98 mm Hg, respectively (eTable 9 in the Supplement). Results from 2 additional reviews focused on specific populations, including participants with treatment-resistant hypertension, are reported in eTable 9 in the Supplement.

Two reviews of positive airway pressure reported on the difference between groups in change from baseline AHI.[37,38] One found a greater reduction in AHI associated with positive airway pressure than with controls (pooled mean difference, −23.41 events per hour [95% CI, −28.51 to −18.30]; 11 trials; n = 832).[37] The second review—which limited inclusion to studies of asymptomatic adults with OSA or studies of minimally symptomatic, nonsleepy adults—found consistent but imprecise pooled estimates (eTable 9 in the Supplement).[38]

Effectiveness of Treatment

Key Question 5. How effective is treatment with positive airway pressure or MADs for improving health outcomes in persons with OSA, including for specific subgroups of interest?

This review included 73 good- or fair-quality RCTs (reported in 87 articles) that reported at least 1 eligible health outcome among groups treated with positive airway pressure or a MADs compared with inactive control.

Positive Airway Pressure

Sixty-three RCTs (74 articles) comparing positive airway pressure with sham positive airway pressure (29 RCTs, 33 articles)[39-71] or another inactive control (34 RCTs, 41 articles)[72-112] reported at least 1 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. Detailed characteristics are reported in eTables 10 and 11 in the Supplement.

Most trials (53) followed up participants for 12 weeks or less; 10 trials followed up participants over a longer duration (16 to 24 weeks [5 trials],[53,78,87,105,111] 52 weeks [3 trials],[74,96,108] a median of 4 years [1 trial],[75] and a median of 4.7 years [1 trial]).[97] 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; 7 enrolled populations with a mean age of 65 years or older.[43,61,79,93,96,97,100] The majority of participants in most trials were men; 1 trial limited enrollment to women,[77] and 3 enrolled a majority of women.[104,109,113] Most trials did not describe the race and ethnicity of enrolled populations, and those that did (14 trials) used heterogeneous categories and varying levels of detail (eTables 10 and 11 in the Supplement). The mean BMI in most trials was 30 to 36 (range, 25-47). The mean or median baseline AHI (or similar measure) for most trials was in the severe OSA range (AHI ≥30); 13 trials reported mean baseline AHI in the moderate OSA range (AHI 16-30),[43,58,61,66,76,80,89,96,97,105,108,109,111] and 6 reported a mean baseline AHI in the mild

Table 3. Summary of Pooled Findings from Positive Airway Pressure Treatment Studies

Outcome measure	No. of trials	No. of participants	Effect size, mean difference (95% CI)	I^2	Estimated MCID
ESS	47	7024	−2.33 (−2.75 to −1.90)	88	−2 to −3[114,115]
SF-36 PCS	13	2031	1.53 (0.29 to 2.77)	59	4 to 7[116,117]
SF-36 MCS	15	2345	2.20 (0.95 to 3.44)	64	4 to 7
Sleep-related QOL					
All measures	17	3083	SMD, 0.30 (0.19 to 0.42)	55	NA[a]
FOSQ only	10	1425	0.55 (0.05 to 1.06)	70	1.8 to 2.2[118]
SAQLI only	6	1725	0.40 (0.17 to 0.62)	81	1 to 2[119]

Abbreviations: ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; MCID, minimal clinically important difference; MCS, mental component summary score; NA, not applicable; PCS, physical component summary score; QOL, quality of life; SAQLI, Sleep Apnea Quality of Life Index; SF-36, 36-Item Short Form Health Survey; SMD, standardized mean difference.

[a] An SMD between 0.2 and 0.4 is considered a small effect size.

OSA range (AHI 5-15).[69,78,81,83,101,107] The severity of OSA for participants enrolled in trials most frequently ranged from moderate to severe (29 trials) or from mild to severe (16 trials). Seventeen trials limited participants to more narrow ranges: mild only,[83,107] mild to moderate or moderate only,[58,69,76,97,100,101,105] or severe only.[40,59,79,91-94,104] One trial did not report sufficient data to determine the range of OSA severity of participants.[78] The mean or median baseline ESS score was 10 or greater in most trials, indicating excessive daytime sleepiness (EDS). Eighteen trials reported a mean baseline ESS score of less than 10,[40, 43, 46, 66, 73-75, 78, 79, 85, 87, 92, 97, 100, 104, 108, 109, 111] and 6 trials did not report a baseline ESS score.

Mortality | Thirty-one RCTs reported on the number of deaths during the study period (eTable 12 in the Supplement). The majority (28 RCTs) reported mortality rates at 24 weeks or less, and most of these (25 RCTs) reported no deaths in any study group (eTable 12 in the Supplement). Two reported on mortality over a median duration of 4 to 5 years; 1 (n = 723) reported 8 deaths in the positive airway pressure group and 3 in the control group (incidence density ratio, 2.6 [95% CI, 0.70-11.8]; $P = .16$),[75] and the second (n = 364) found a similar number of deaths among the positive airway pressure and control groups (8% vs 7%, respectively).[97]

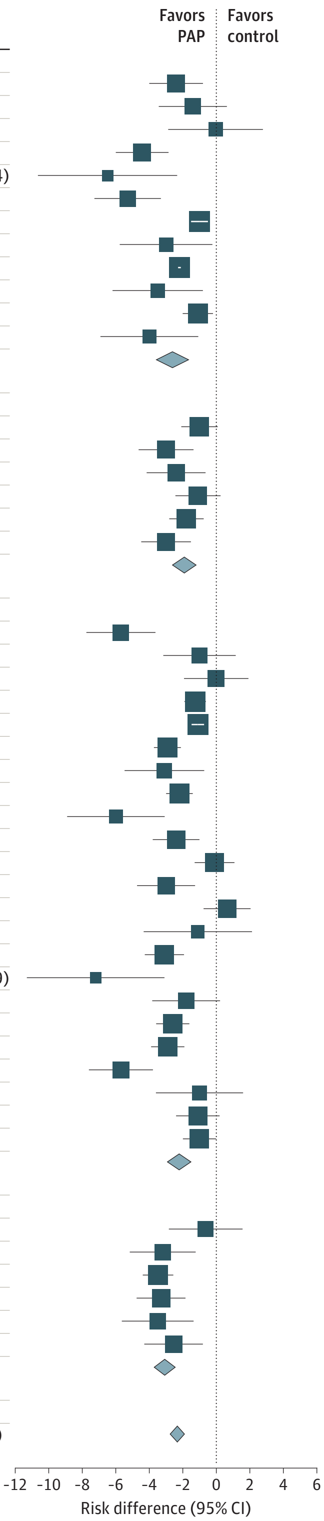
General Health–Related QOL | Twenty RCTs reported on QOL using the 36-Item Short Form Health Survey (SF-36)[40, 46, 50, 59, 60, 67-69, 76, 78, 83, 86, 89, 94, 96, 105, 107, 108, 111, 112]; most trials reported changes on the SF-36 physical component summary score and the mental component summary score. Pooled estimates in change from baseline SF-36 mental component summary score found a significantly greater improvement associated with positive airway pressure compared with inactive control (2.20 [95% CI, 0.95-3.44]; 15 trials; n = 2345).[40, 46, 50, 60, 67-69, 78, 86, 94, 105, 107, 108, 111, 112] Similarly, pooled estimates for change in SF-36 physical component summary score from baseline found significantly greater improvement associated with positive airway pressure than with control (1.53 [95% CI, 0.29-2.77]; 13 trials; n = 2031 participants) (**Table 3**; eFigure 1 in the Supplement).[40,46,50,60,67-69,86,94,107,108,111,112] The pooled estimates for change from baseline SF-36 mental component summary score and SF-36 physical component summary score associated with positive airway pressure were smaller than the range considered a minimal clinically important difference (MCID), which is 4 to 7 for both SF-36 component summary scores.[116,117] Few RCTs reported on other measures of QOL. Few studies reported on other QOL measures; overall, results were mixed (eTable 12 in the Supplement).

Sleep-Related QOL | Seventeen RCTs assessed sleep-related QOL: 6 using the Sleep Apnea Quality of Life Index (SAQLI),[54,67,70,78,89,96] 10 using the Functional Outcomes of Sleep Questionnaire (FOSQ),[40,58-60,65,69,76,84,94,107,111] and 1 using the Quebec Sleep Questionnaire.[79] The meta-analysis (combining all measures) found that positive airway pressure was associated with a small but statistically significant improvement in sleep-related QOL compared with controls (SMD, 0.30 [95% CI, 0.19-0.42]; 17 trials; n = 3083) (eFigure 2 in the Supplement). The subgroup analysis by mean baseline ESS score found a similar but slightly larger effect size in trials with a mean ESS score of 10 or greater (SMD, 0.35 [95% CI, 0.22-0.49]; 11 trials, n = 2228). In studies with a mean baseline ESS score of less than 10, the effect size was smaller and the pooled estimate was not statistically significant (eFigure 4 in the Supplement). Results shown as a mean difference in scores for each sleep-related QOL measure are provided in eFigure 3 in the Supplement and summarized in Table 3. For both the SAQLI and FOSQ, the pooled mean difference falls below the range considered an MCID.

ESS Score | Forty-seven trials reported sufficient ESS data to include in meta-analyses. Most were 12 weeks or less in duration; 7 followed up participants for 24 weeks,[53,105,111] 48 to 52 weeks,[74,96,108] or longer.[75] The meta-analyses found that positive airway pressure reduced mean ESS scores more than controls (pooled mean difference, −2.33 [95% CI, −2.75 to −1.90]; 47 trials; n = 7024) (**Figure 3**). The pooled mean difference is within the range considered an MCID for the ESS (−2 to −3).[114,115] These analyses found substantial statistical heterogeneity that may be due to variation in positive airway pressure devices, participant characteristics (eg, baseline ESS score), treatment adherence, study duration, or chance; however, no clear explanation was found. As shown in Figure 3, heterogeneity is lower in subgroups defined by narrow ranges of OSA severity (severe only and mild only or mild to moderate vs mild to 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

Figure 3. Comparison of Positive Airway Pressure vs Inactive Control for Change in ESS

Source	No. of participants	Duration, wk	Comparator	Baseline ESS score	Mean difference (95% CI)
Mild to severe OSA					
Campos-Rodriguez et al,[41] 2006	72	4	Sham	15	-2.40 (-4.01 to -0.79)
Egea et al,[46] 2008	45	12	Sham	8	-1.40 (-3.44 to 0.64)
Hui et al,[49] 2006	56	12	Sham	11	-0.04 (-2.88 to 2.80)
Jackson et al,[87] 2021	121	16	Control	8	-4.43 (-6.01 to -2.85)
Jenkinson et al,[50] 1999	107	4	Sham	17	-6.50 (-10.66 to -2.34)
Kohler et al,[64] 2008	102	4	Sham	16	-5.30 (-7.29 to -3.31)
Kushida et al,[53] 2012	1105	24	Sham	10	-1.00 (-1.50 to -0.50)
Lam et al,[89] 2007	67	10	Control	12	-3.00 (-5.77 to -0.23)
McMillan et al,[96] 2014	278	52	Control	12	-2.20 (-2.28 to -2.12)
Ng et al,[109] 2018	37	12	Control	8-10	-3.50 (-6.20 to -0.80)
Robinson et al,[66] 2006	70	4	Sham	5	-1.10 (-2.00 to -0.20)
West et al,[70] 2007	42	12	Sham	15	-4.00 (-6.93 to -1.07)
Total					-2.61 (-3.57 to -1.66)
Heterogeneity: I^2 = 89.9%					
Mild only, or mild to moderate OSA					
Barnes et al,[76] 2004	228	12	Control	11	-1.00 (-2.09 to 0.09)
Engleman et al,[83] 1999	74	4	Control	13	-3.00 (-4.64 to -1.36)
Marshall et al,[58] 2005	62	3	Sham	13	-2.40 (-4.16 to -0.64)
Redline et al,[101] 1998	111	8-12	Control	11	-1.09 (-2.44 to 0.26)
Weaver et al,[69] 2012	239	8	Sham	15	-1.78 (-2.81 to -0.75)
Wimms et al,[107] 2020	233	12	Control	10	-3.00 (-4.48 to -1.52)
Total					-1.91 (-2.61 to -1.20)
Heterogeneity: I^2 = 39.1%					
Moderate only, or moderate to severe OSA					
Ballester et al,[72] 1999	105	12	Control	12	-5.70 (-7.77 to -3.63)
Banghøj et al,[73] 2020	72	12	Control	7	-1.00 (-3.17 to 1.17)
Barbé et al,[40] 2001	55	6	Sham	7	0.00 (-1.93 to 1.93)
Barbé et al,[74] 2010	55	52	Control	6	-1.26 (-1.91 to -0.61)
Barbé et al,[75] 2012	723	208	Control	7	-1.10 (-1.48 to -0.72)
Campos-Rodriguez et al,[77] 2016	307	12	Control	10	-2.92 (-3.73 to -2.11)
Coughlin et al,[44] 2007	70	6	Sham	14	-3.10 (-5.48 to -0.72)
Durán-Cantolla et al,[45] 2010	340	12	Sham	10	-2.20 (-3.00 to -1.40)
Engleman et al,[82] 1998	46	4	Control	12	-6.00 (-8.92 to -3.08)
Faccenda et al,[84] 2001	142	4	Control	15	-2.40 (-3.80 to -1.00)
Hoyos et al,[48] 2012	65	12	Sham	10	-0.10 (-1.29 to 1.09)
Jones et al,[52] 2013	106	12	Sham	13	-3.00 (-4.74 to -1.26)
Lam et al,[55] 2010	61	1	Sham	11	0.65 (-0.76 to 2.06)
Loredo et al,[57] 2006	41	2	Sham	12	-1.10 (-4.34 to 2.14)
Martínez-García et al,[92] 2013	194	12	Control	9	-3.10 (-4.27 to -1.93)
Montserrat et al,[60] 2001	48	6	Sham	17	-7.21 (-11.33 to -3.09)
Phillips et al,[65] 2011	76	8	Sham	10	-1.80 (-3.83 to 0.23)
Ponce et al,[100] 2019	145	12	Control	9	-2.60 (-3.59 to -1.61)
Shaw et al,[105] 2016	298	24	Control	10	-2.90 (-3.90 to -1.90)
Siccoli et al,[67] 2008	102	4	Sham	16	-5.70 (-7.62 to -3.78)
Smith et al,[68] 2007	52	6	Sham	10	-1.00 (-3.61 to 1.61)
Traaen et al,[111] 2021	108	24	Control	8	-1.10 (-2.40 to 0.20)
Zhao et al,[108] 2017	169	48	Control	8	-1.00 (-1.99 to -0.01)
Total					-2.21 (-2.92 to -1.51)
Heterogeneity: I^2 = 87.2%					
Severe OSA					
Dalmases et al,[79] 2015	31	12	Control	6-8	-0.63 (-2.83 to 1.57)
Lui et al,[91] 2020	90	4	Control	11	-3.20 (-5.17 to -1.23)
Martínez-García et al,[93] 2015	224	12	Control	10	-3.48 (-4.39 to -2.57)
Masa et al,[94] 2015	150	8	Control	11	-3.30 (-4.76 to -1.84)
Melehan et al,[59] 2018	20	12	Sham	10	-3.50 (-5.65 to -1.35)
Salord et al,[104] 2016	80	12	Control	8	-2.55 (-4.30 to -0.80)
Total					-3.08 (-3.71 to -2.45)
Heterogeneity: I^2 = 2.7%					
Overall					
Heterogeneity: I^2 = 88.3%					-2.33 (-2.75 to -1.90)



ESS indicates Epworth Sleepiness Scale; OSA, obstructive sleep apnea; PAP, positive airway pressure.

score change were −2.61 for mild to severe, −1.91 for mild only and mild to moderate, −2.21 for moderate only and moderate to severe, and −3.08 for severe only, and CIs overlapped; the analysis still found considerable statistical heterogeneity within the mild to severe group and the moderate only or moderate to severe group (Figure 3).

Other Health Outcomes | Fewer studies reported on other health outcomes (eTable 12 in the Supplement). Three RCTs reported on the incidence of motor vehicle crashes over 12 to 52 weeks, and none found a statistically significant difference between groups.[53,85,96] Ten reported on the incidence of 1 or more heterogeneous cardiovascular outcomes.[46,53,58,70,75,78,85,96,97,111] Six RCTs (1773 total participants) reported on the incidence of myocardial infarction; in 4 of these, a total of 1 myocardial infarction occurred (combined) in either group over 3 weeks to 1 year.[58,78,85,96] Two RCTs reported on outcomes over a median of 4 to 5 years; 1 (n = 723) reported 2 myocardial infarctions in the positive airway pressure group and 8 in the control group,[75] and the second (n = 244) found a similar number of myocardial infarctions in the positive airway pressure and control groups (9% vs 7%, respectively).[97]

RCTs reporting on other health outcomes (eg, angina, transient ischemic attacks, measures of cognitive impairment) are shown in eTable 12 in the Supplement. Overall, too few events occurred to draw conclusions.

Mandibular Advancement Devices

Twelve RCTs (15 articles) evaluated the benefit of MADs for improving health outcomes (eTable 13 in the Supplement).[76,89,120-132] Four studies compared MADs with sham devices that did not advance the mandible,[120,121,130-132] 1 compared a MAD with a placebo tablet,[76] 2 compared MADs with no treatment,[123,129] and 1 compared a MAD with conservative management of OSA with weight loss.[89] All studies recruited participants with known or suspected OSA from specialty clinics, such as sleep medicine or otolaryngology. Treatment durations ranged from 4 to 12 weeks for most studies; however, 1 lasted for only 1 week[123] and 1 for 24 weeks.[120,121] The mean age of enrolled participants ranged from 46 to 58 years. In 11 trials reporting on sex, the majority of participants were men. No study reported the percentage of minority participants. Almost all studies included participants with mild to moderate OSA, and 6 also included participants with severe OSA.[89,122,123,125,128,132]

Mortality | Four trials reported on deaths in each group over 1 to 12 weeks of follow-up,[76,123,129,132] 3 reported no participant deaths, and 1 reported a single death in the control group.[132]

General Health–Related and Sleep-Related QOL | Six RCTs reported on at least 1 QOL measure.[76,89,120,121,129,131,132] Overall, results were mixed, with some studies finding no significant improvement in QOL from using MADs,[89,120,121,131] some reporting possible benefits for some measures or subscales but not for others,[76,132] and some reporting benefits for some overall QOL scores.[129] Further details and specific data are provided in eTable 14 in the Supplement. Because of inconsistency, imprecision, and heterogeneity of reporting, findings are insufficient to make conclusions about the potential benefits of using MADs for improving QOL.

ESS Score | Ten RCTs of MADs provided sufficient data on change from ESS scores from baseline to be included in pooled estimates[76,89,122-125,128-130,132]; MADs were associated with significantly greater reduction from baseline ESS scores than controls (−1.67 [95% CI, −2.09 to −1.25]; 10 trials; n = 1540 participants) (eFigure 5 in the Supplement). The pooled mean difference, however, falls below the range considered an MCID for the ESS.[114,115]

Other Health Outcomes | This review included 1 trial assessing each of the following outcomes for participants using MADs over 6 to 12 weeks: cognitive impairment,[76] motor vehicle crashes,[129] cardiovascular events,[129] and headaches.[131] Specific data are provided in eTable 14 in the Supplement. Because of unknown consistency, imprecision, and very small numbers of events, findings were insufficient to make conclusions about the potential benefits of MADs for these outcomes.

Harms of Treatment

Key Question 6. What are the harms associated with treatment of OSA using positive airway pressure or MADs, including for specific subgroups of interest?

Reporting of harms in the included RCTs was sparse, and most did not report information on harms. Nineteen RCTs (reported in 24 articles) reported on harms associated with treatment of OSA, including 9 trials of positive airway pressure,[49,53,54,68,69,83,89,101,105,113,133,134] 9 of MADs,[89,120,121,123-132] and 1 of positive airway pressure and MADs.[89] Characteristics and detailed results of all 19 studies reporting harms are provided in eTables 10, 11, 13, 15, and 16 in the Supplement.

Positive Airway Pressure

Of the 10 included RCTs of positive airway pressure, 6 compared positive airway pressure with a sham device,[49,53,54,68,69,113,133,134] and 4 compared positive airway pressure with another control (eg, oral placebo, usual care).[83,89,101,105] Most enrolled fewer than 100 persons; 1 trial, the Apnea Positive Pressure Long-term Efficacy Study,[53,54] enrolled more than 1000 participants. The majority of participants were men, the mean age ranged from 42 to 62 years, and most participants were overweight or obese (mean BMI, 27-39). Most of the studies followed up patients for 8 to 12 weeks, and 2 lasted 24 weeks.[53,54,105]

Outcomes reported were heterogeneous, and detailed results are reported in eTable 15 in the Supplement. In general, harms related to positive airway pressure treatment were likely short-lived and could have been alleviated by discontinuing treatment with positive airway pressure or by supplementing positive airway pressure with additional interventions. Overall, 1% to 47% of participants in trials of positive airway pressure reporting any harms had specific adverse events while using positive airway pressure, including claustrophobia, oral or nasal dryness, eye or skin irritation, rash, nosebleeds, and pain.

Mandibular Advancement Devices

Ten RCTs reported harms related to MAD use.[89,120,121,123-132] Most RCTs (6) lasted 4 to 8 weeks, 1 lasted a single week,[123] 1 lasted 10 weeks,[89] 1 lasted 12 weeks,[124] and 1 lasted 24 weeks.[120,121] Across 3 studies that reported any discontinuation of treatment because of adverse events, 7% of patients in the active MAD group discontinued MAD use because of harms compared with 1% of patients in the control group.[89,129,132] In 4 RCTs, rates of oral dryness ranged from 5% to 33% in the active MAD group compared with 0% to 3% in the control group.[89,120,121,124,129] Six studies reported rates of excess salivation.[89,120,121,124-127,129,131] Four trials reported significantly higher rates of excessive salivation associated with MAD use than with sham MAD or no treatment,[89,120,121,129] In 7 studies, adverse oral mucosal, dental, or jaw symptoms ranged from 17% to 74% in MAD groups compared with 0% to 17% 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.[125-127,131]

Discussion

This systematic review synthesized evidence relevant to screening for OSA in adults. **Table 4** summarizes findings, including an assessment of the strength of evidence for each KQ. To date, there is no direct evidence from trials on the benefits and harms of screening for OSA vs no screening. Potential harms of routine screening include overdiagnosis and overtreatment for asymptomatic persons with OSA (AHI ≥5) who never had symptoms of OSA or adverse health outcomes from OSA. Other potential harms include costs associated with referrals and additional testing (eg, future polysomnography for follow-up care).

This review identified 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 included screening approach was assessed by more than 2 included studies, which limits the ability to draw conclusions about the accuracy of screening tools in primary care. The screening approach evaluated by 2 studies, the MVAP score followed by an unattended home sleep test for detecting severe OSAS (AHI ≥30 and ESS score >10), may have promise for screening, but the evidence was limited by potential spectrum bias[135-139] due to oversampling of high-risk participants and of those with OSA and OSAS, which may substantially overestimate the accuracy of using the MVAP score to screen for OSA in the general population. The included studies evaluating MVAP enrolled populations with a high prevalence of OSAS (≥25%),[23,24] OSA (AHI ≥5 for 80% of participants),[24] and sleepiness (74%).[23]

This review included fewer studies evaluating questionnaires or clinical prediction tools than some previously published reviews and guidelines,[9,140,141] primarily because of the requirement to include studies that enrolled asymptomatic adults or adults with unrecognized symptoms of OSA; referral populations (eg, 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 and strength of evidence for questionnaires and prediction tools.

This review found consistent evidence from good- and fair-quality RCTs that positive airway pressure reduces excessive daytime sleepiness and may improve general health–related and sleep-related QOL. However, benefit associated with positive airway pressure for both general health–related 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, the data suggest a clinically significant reduction in most included trials because 85% of the trials in the meta-analysis for ESS with mean baseline ESS scores of 10 or greater (indicating excessive daytime sleepiness) reported mean end point ESS scores in the normal range of less than 10[142,143] for the positive airway pressure groups (mean end point ESS score <8). However, the threshold for a clinically significant change in ESS score is somewhat uncertain. Although recent systematic reviews noted that experts consider a 1-point change in ESS score clinically significant,[9] other sources suggest that a 2- to 3-point change[114,115] or a 3- to 4-point change should be the clinically significant threshold for its sample size calculations or interpretation of findings.[144-146] Also, the American College of Chest Physicians' outcome experts evaluating the ESS informally stated that a clinically significant change in the ESS score probably is at least 3 points and cited a specific example that a reduction of 1 point (eg, from 3 [high] to 2 [moderate]) on 2 of 7 ESS domains was unlikely to be clinically relevant (Jon-Erik C. Holty, MD, MS, Stanford University, email, October 2015). Regardless of the clinically significant threshold level, the subjective nature of the ESS creates potential bias in trials of treatment (eg, overreporting of improvements in sleepiness after receiving treatment), and some authors have raised concerns about its construct validity (ie, authors have expressed uncertainty regarding whether it is an accurate measure of sleepiness).[147-149]

For blood pressure reduction (KQ4), recent systematic reviews found that MAD and positive airway pressure are associated with a reduction in blood pressure of 2 to 3 mm Hg, and 1 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 mm Hg systolic/10 mm Hg diastolic is clinically meaningful for patients.[150-152] However, guidelines have suggested that across a population, a smaller reduction in systolic blood pressure (2-3 mm Hg) could result in a clinically significant reduction in cardiovascular mortality (4%-5% for coronary heart disease and 6%-8% for stroke).[153] Even though MADs and positive airway pressure have been shown to reduce mean blood pressure, no trial to date has shown a significant reduction in mortality or cardiovascular disease.

Evidence on most health outcomes was limited (ie, too few RCTs reported on outcomes or too few events occurred to evaluate the effectiveness of positive airway pressure for reducing mortality or motor vehicle crashes). As summarized in the eContextual Questions in the Supplement, a relatively large body of observational evidence supports an association between severe OSA and increased risk of many adverse health outcomes, including cardiovascular events, mortality, and cognitive impairment. Some observational 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. In addition, findings of increased risk associated with severe OSA are the strongest among male populations; however, it is difficult to assess whether these relationships do not hold for female populations or reflect sparse evidence on female populations compared with male populations. Observational studies focused on this association are limited, however, primarily owing to potential confounding.

Reporting of harms from treatment in the included studies was sparse. In general, the adverse events related to positive airway pressure treatment were likely short-lived and could have been alleviated by discontinuing treatment with positive airway pressure or by supplementing positive airway pressure with additional interventions.

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

Questionnaire, prediction tool, test, or intervention	No. of studies and study design (total sample size) by test or outcome	Summary of findings by test or outcome	Consistency and precision	Reporting bias	Study quality	Body of evidence limitations	Overall strength of evidence	Applicability
KQ1: Benefits of screening								
None	0	No eligible study	NA	NA	NA	NA	Insufficient	NA
KQ2: Accuracy of screening questionnaires, clinical prediction tools, and multistep screening approaches								
Berlin Questionnaire	2 Cross-sectional studies (563)	Varies by OSA threshold (AHI cut point) Sensitivity, 37%-94% Specificity, 0%-84%	Unknown consistency: studies used different reference test thresholds Unknown precision: 1 study reported CIs (precise) and 1 did not report CIs)	Undetected	Fair	Studies enrolled different populations; 1 with risk of bias due to attrition bias and spectrum bias, and 1 (enrolling US adults with type 2 diabetes) with small sample size and risk of bias due to unclear methods for calculating accuracy of OSA categories	Insufficient	Unclear: 1 study enrolled general population of Norway and 1 enrolled US adults with type 2 diabetes
STOP-BANG	2 Cross-sectional studies (245)	Varies by OSA threshold (AHI cut point) Sensitivity, 87%-94% Specificity, 0%-38%	Unknown consistency: studies used different reference test thresholds Unknown precision: 1 study reported CIs (precise) and 1 did not report CIs	Undetected	Fair	Studies enrolled different populations: 1 with type 2 diabetes and 1 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 type 2 diabetes and taking opioids for chronic pain
Modified STOP-BANG[a]	1 Cross-sectional study (91)	AHI >30: Sensitivity, 61% (95% CI, 4% to 74%) Specificity, 76% (95% CI, 59% to 89%)	Unknown consistency (single study) Imprecise	Undetected	Fair	Single study with risk of bias due to patient selection	Insufficient	Persons with Alzheimer disease

(continued)

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

Questionnaire, prediction tool, test, or intervention	No. of studies and study design (total sample size) by test or outcome	Summary of findings by test or outcome	Consistency and precision	Reporting bias	Study quality	Body of evidence limitations	Overall strength of evidence	Applicability
Modified STOP-BANG[b]	1 Cross-sectional study (199)	AHI ≥5: Sensitivity, 93% (95% CI, 88% to 96%) Specificity, 32% (95% CI, 24% to 37%) AHI ≥15: Sensitivity, 95% (95% CI, 88% to 99%) Specificity, 23% (95% CI, 19% to 25%) AHI >30: Sensitivity, 100% (95% CI, 89% to 100%) Specificity, 21% (95% CI, 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 taking opioids for chronic pain
MVAP score (for severe OSAS)	2 Cross-sectional studies (702)	For severe OSAS (AHI ≥30 and ESS >10) using MVAP cutoff 0.48-0.49: Sensitivity, 90%-91.5% (95% CI NR) Specificity, 43.9%-64.4% (95% CI NR) AUC, 0.68 (95% CI, 0.67 to 0.70) to 0.78 (95% CI, 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 study	Insufficient	Populations with high prevalence of OSAS (≥25%); only 1 study reported % with any OSA (80%); studies included Medicare recipients and adults with hypertension
MVAP score (for any OSAS)	1 Cross-sectional study (250)	For any OSAS (AHI ≥5 and ESS >10): Sensitivity, 69.4% (95% CI NR) Specificity, 56.5% (95% CI NR) AUC, 0.614 (95% CI 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 hypertension
MVAP score followed by unattended; HST (for severe OSAS)	2 Cross-sectional studies (702)	For severe OSAS (AHI ≥30 and ESS >10) using home-based AHI of 15 or 18: Sensitivity, 88.2%-90.9% (95% CI NR) Specificity, 71.6%-75.7% (95% CI NR) AUC, 0.799 (95% CI, 0.777 to 0.822) and 0.833 (95% CI, 0.765 to 0.902)	Consistent Precise	Undetected	Fair	Concern for spectrum bias in both studies; risk of attrition bias in 1 study	Low	Populations with high prevalence of OSAS; studies included Medicare recipients and adults with hypertension
MVAP score followed by unattended HST (for any OSAS)	1 Cross-sectional study (250)	For any OSAS (AHI ≥5 and ESS >10): Sensitivity, 80.5% (95% CI NR) Specificity, 54.0% (95% CI NR) AUC, 0.672 (95% CI 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 hypertension
KQ3: Harms associated with screening or subsequent diagnostic testing								
None	0	No eligible study	NA	NA	NA	NA	Insufficient	NA

(continued)

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

Questionnaire, prediction tool, test, or intervention	No. of studies and study design (total sample size) by test or outcome	Summary of findings by test or outcome	Consistency and precision	Reporting bias	Study quality	Body of evidence limitations	Overall strength of evidence	Applicability
KQ4: Efficacy of treatment for improving intermediate outcomes								
Positive airway pressure	AHI: 2 systematic reviews: 1 focused on any OSA severity (11 RCTs; 832) participants) and 1 limited to nonsleepy populations (3 RCTs; 1541 participants) Blood pressure: 3 systematic reviews: 1 focused on any OSA severity (12 RCTs; 1919 participants), 1 limited to nonsleepy populations (5 RCTs; 1541 participants), and 1 limited to populations with resistant hypertension (23 RCTs; 4905 participants)	AHI, pooled mean difference: Any OSA severity, −23.41 (95% CI, −28.51 to −18.30); I^2 = 93% Nonsleepy populations, −15.57 (95% CI, −29.32 to −1.82); I^2 = 87.2% Daytime blood pressure, pooled mean difference: Any OSA severity: SBP, −2.76 (95% CI, −4.31 to −1.20); I^2 = 5%; DBP, −1.98 (95% CI, −3.02 to −0.93); I^2 = 4%[c] Nonsleepy populations: SBP, −0.51 (95% CI, −3.39 to 2.38); I^2 = 84%; DBP, −0.92 (95% CI, −1.39 to −0.46); I^2 = 0.0% Populations with resistant hypertension: Mean 24-h SBP, −5.06 (95% CI, −7.98 to −2.13); mean 24-h DBP, −4.21 (95% CI, −6.50 to −1.93)	Consistent for AHI and blood pressure Precise for AHI and blood pressure; imprecise for blood pressure in pooled estimate limited to nonsleepy populations	Undetected	Good[d]	Most trials were ≤12 wk; estimates associated with significant heterogeneity	Moderate for AHI and blood pressure in overall (any) OSA populations and populations with resistant hypertension; low for blood pressure in nonsleepy populations	Referral population with known OSA
MADs	Blood pressure: 1 systematic review (11 RCTs; 469 participants)	No statistically significant reduction in daytime, nighttime, or 24-h blood pressure measures	Consistent Imprecise	Undetected	Good[d]	Variations in blood pressure treatment at baseline and limited follow-up (1-3 mo)	Low	Referral population with known OSA
KQ5: Efficacy of treatment for improving health outcomes								
Positive airway pressure[e]	Mortality: 31 RCTs (2673) ESS: 47 RCTs (7024) SF-36 PCS: 13 RCTs (2031) SF-36 MCS: 15 RCTs (2345) Sleep-related QOL (SAQLI, FOSQ, or QSQ): 17 RCTs (3083) Cardiovascular events: 8 RCTs (1529)	Mortality: no event (27 RCTs) or 1 event (2 RCTs) at ≤12 wk; no significant difference at 24 wk (1 RCT: 2 vs 2), median of 4 y (1 RCT: 8 vs 3), or median of 5 y ESS: pooled mean difference, −2.33 (95% CI, −2.75 to −1.90) SF-36 PCS: positive airway pressure vs any comparator; mean difference, 1.53 (95% CI, 0.29 to 2.77) SF-36 MCS: positive airway pressure vs any comparator; mean difference, 2.20 (95% CI, 0.95 to 3.44) SAQLI or FOSQ: positive airway pressure vs any comparator; SMD, 0.30 (95% CI, 0.19 to 0.42) Cardiovascular events: overall, too few events were observed to draw conclusions	Mortality and cardiovascular events: Consistent for RCTs of relatively short duration (≤12-24 wk), unknown for longer duration Imprecise ESS: Consistent Precise SF-36 PCS and 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 (eg, mortality, cardiovascular events)	Moderate for sleep-related QOL and ESS, low for general health- related QOL; insufficient for other health outcomes	Referral population with known OSA

(continued)

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

Questionnaire, prediction tool, test, or intervention	No. of studies and study design (total sample size) by test or outcome	Summary of findings by test or outcome	Consistency and precision	Reporting bias	Study quality	Body of evidence limitations	Overall strength of evidence	Applicability
MADs[e]	Mortality: 4 RCTs (245) ESS: 10 RCTs (1540) 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-wk RCT (n = 93) QOL measures: mixed results	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 wk), small number of studies reporting the outcomes and too few events (for mortality and motor vehicle crashes)	Moderate for ESS; insufficient for other outcomes	Referral population with known OSA
KQ6: Harms associated with treatment								
Positive airway pressure	10 RCTs (2064)	Overall, 1% to 47% had specific adverse events while using positive airway pressure 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
MADs	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

Abbreviations: AHI, apnea-hypopnea index; AUC, area under the curve; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; HST, home sleep test; KQ, key question; MAD, mandibular advancement device; MCS, mental component summary score; MVAP, Multivariable Apnea Prediction; NA, not applicable; NR, not reported; OSA, obstructive sleep apnea; OSAS, obstructive sleep apnea syndrome; PCS, physical component summary score; QOL, quality of life; QSQ, Quebec Sleep Questionnaire; RCT, randomized clinical trial; SAQLI, Sleep Apnea Quality of Life Index; SBP, systolic blood pressure; SF-36, 36-Item Short Form Health Survey; SMD, standardized mean difference; STOP-BANG, snoring, tiredness, observed apnea, blood pressure, body mass index, age, neck circumference, gender.

[a] Modified STOP-BANG (age >70 years; body mass index ≥26; neck circumference >26.5 cm).

[b] Modified STOP-BANG (age 5-64 years, 1 point; age ≥65 years, 2 points; and waist circumference >85, snoring; observed apnea; high blood pressure; body mass index >25; each 1 point).

[c] Pooled estimates were similar for nighttime and 24-hour blood pressure outcomes and for subgroup analyses of populations with hypertension and resistant hypertension.

[d] Study quality rating refers to quality of the systematic reviews, not the quality of individual trials included by the reviews.

[e] Selected results for the most commonly reported outcomes are included in this table. Details on additional measures (eg, Nottingham Health Profile) with few studies and insufficient evidence to draw conclusions are provided in the text and appendices.

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.

Evidence included in the current review suggests several important research needs. To better understand the potential effectiveness of screening for OSA, RCTs of asymptomatic persons (or those with unrecognized symptoms of OSA) that directly compare screening with no screening and assess health outcomes are needed. To better determine the accuracy of screening questionnaires and clinical prediction tools when used in the general population (related to KQ2), 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 (eg, MVAP followed by an unattended home sleep test) as well as other approaches assessed in similar populations for which there were few studies, such as the Berlin Questionnaire and STOP-BANG questionnaire. Trials of treatment (positive airway pressure and MAD) that enroll participants who are screen-detected in primary care settings are needed; results of trials that enroll participants referred for OSA symptoms and other sleep issues may not be applicable to populations who are screen-detected.

Limitations

This review has several limitations. First, studies of screening accuracy were required to have used in-laboratory polysomnography as the reference standard. This is similar to the approach used in previous systematic reviews. Second, studies that focused on the benefits and harms of treatment were limited to studies of interventions considered first-line treatment for persons with newly detected OSA (positive airway pressure and MAD); studies of interventions primarily offered to persons who do not benefit from or tolerate positive airway pressure or MAD were excluded. Third, some of the meta-analyses of RCTs evaluating the benefits of positive airway pressure (KQ5) found substantial statistical heterogeneity. Although a clear explanation for all statistical heterogeneity was not found, possible explanations include variation in enrolled populations, positive airway pressure devices (eg, machines, masks, humidifiers, filters, cushions), apnea and hypopnea definitions, adherence, study duration, study methods, or chance.

Conclusions

The accuracy and clinical utility of OSA screening tools that could be used in primary care settings were uncertain. Positive airway pressure and mandibular advancement devices reduced ESS score. Trials of positive airway pressure found modest improvement in sleep-related and general health–related QOL but have not established whether treatment reduces mortality or improves most other health outcomes.

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