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An Official American Thoracic Society Research Statement: Impact of Mild Obstructive Sleep Apnea in Adults

Executive Summary

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Background: Mild obstructive sleep apnea (OSA) is a highly prevalent disorder in adults; however, whether mild OSA has significant neurocognitive and cardiovascular complications is uncertain.

Objectives: The specific goals of this Research Statement are to appraise the evidence regarding whether long-term adverse neurocognitive and cardiovascular outcomes are attributable to mild OSA in adults, evaluate whether or not treatment of mild OSA is effective at preventing or reducing these adverse neurocognitive and cardiovascular outcomes, delineate the key research gaps, and provide direction for future research agendas.

Methods: Literature searches from multiple reference databases were performed using medical subject headings and text words for OSA in adults as well as by hand searches. Pragmatic systematic reviews of the relevant body of evidence were performed.

Results: Studies were incongruent in their definitions of "mild" OSA. Data were inconsistent regarding the relationship between mild OSA and daytime sleepiness. However, treatment of mild OSA may improve sleepiness in patients who are sleepy at baseline and improve quality of life. There is limited or inconsistent evidence pertaining to the impact of therapy of mild OSA on neurocognition, mood, vehicle accidents, cardiovascular events, stroke, and arrhythmias.

Conclusions: There is evidence that treatment of mild OSA in individuals who demonstrate subjective sleepiness may be beneficial. Treatment may also improve quality of life. Future research agendas should focus on clarifying the effect of mild OSA and impact of effective treatment on other neurocognitive and cardiovascular endpoints as detailed in the document.

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Overview

Mild obstructive sleep apnea (OSA) is a highly prevalent disorder in adults. However, whether mild OSA has significant neurocognitive and cardiovascular complications is uncertain. This Research Statement appraises the evidence regarding whether or not long-term adverse neurocognitive and cardiovascular outcomes are attributable to mild OSA in adults, determines whether or not treatment of mild OSA is effective at preventing or reducing these adverse neurocognitive and cardiovascular outcomes, delineates the key research gaps, and provides direction for future research agendas.

- In this research statement, mild OSA was identified when the metric of OSA severity (apnea–hypopnea index, respiratory disturbance index, or oxygen desaturation index) in the sleep study was at least 5/h and less than 15/h.
- Most randomized controlled trials with continuous positive airway pressure (CPAP) demonstrate that treatment of mild OSA improves subjective assessments of daytime sleepiness by a small amount and that this effect may only be present in patients with an elevated level of sleepiness at baseline. However, limited existing data show no impact of treatment on objective measures of sleepiness. The impact of non–positive airway pressure (PAP) therapies on daytime sleepiness remains unclear.
- A limited number of population-based and clinic-based studies provide conflicting data regarding the risk of motor vehicle accidents as a consequence of mild OSA. There are no studies on the impact of treatment of mild OSA on the risk for motor vehicle accidents.
- Although the few studies that have evaluated the impact of mild OSA on quality of life have yielded conflicting results, most studies seem to show a small improvement in quality of life after treatment of OSA.
- In the absence of population-based studies, limited clinic-based data do not provide evidence of an association between mild OSA and neurocognitive function. Clinical trials are not consistent on which measures of neurocognitive function, if any, improve as a result of treatment for mild OSA.
- There are discordant data examining the association between mild OSA and mood, as well as limited data regarding the effect of treatment of mild OSA on mood.
- It is unclear whether there is an association between mild OSA and increased incidence of cardiovascular events. It is unclear whether there is a differential impact of mild OSA on hypertension and cardiovascular complications in high-risk populations (e.g., individuals with underlying cardiovascular disease or multiple comorbid conditions) as well as those who are sleepy.
- Mild OSA is likely not associated with an increase in stroke in subjects from the general population or patients referred for sleep studies. However, limited data suggest that mild OSA may increase stroke risk in persons with underlying coronary artery disease.
- It is not clear whether an association exists between mild OSA and the risk for developing atrial fibrillation and other arrhythmias.
- Available evidence from population-based longitudinal studies indicates that mild OSA is not associated with increased cardiovascular or all-cause mortality. There are no studies of the impact of treatment on cardiovascular mortality. There was no evidence from a single study that treatment of mild OSA reduces all-cause mortality.
- The task force members identified specific research gaps and made recommendations to address these gaps in knowledge. These are detailed in Tables 6 and 7, respectively.

Introduction

OSA is a major public health problem that is characterized by repetitive obstruction of the upper airway resulting in oxygen desaturation and/or arousals from sleep (1). The prevalence of OSA syndrome defined as apnea–hypopnea index (AHI) greater than or equal to 5/h with daytime sleepiness ranges from 3 to 7.5% in adult men and from 2 to 3% in adult women (2–8) (AHI: number of apneas and hypopneas per hour of sleep). Additionally, a significant proportion of the populace has mild OSA, defined as AHI 5/h to less than 15/h (9). One estimate of mild OSA prevalence in the general population is 7.6% in men and 15% in women, respectively (7).

Although there is clear evidence linking severe OSA to adverse cardiovascular and neurocognitive sequelae (10–17), whether mild OSA has negative impact on health is controversial (18–20). A 2011 Agency for Health Care Research and Quality report (21) noted a lack of clarity regarding the impact of mild OSA on long-term neurocognitive, cardiovascular, and functional outcomes. It is also not clear whether treatment of mild OSA with positive airway pressure (PAP) or alternative modalities improves clinical outcomes.

Purpose

The overarching goal of this Research Statement is to provide a state-of-the-art critical appraisal of the evidence describing the neurocognitive and cardiovascular sequelae of mild OSA and the effects of treatment of mild OSA, to identify research gaps, and to provide recommendations for conducting future research.

See the full-length online version and the online supplement for details of methods and results.

Methods

An international task force of sleep clinicians and investigators developed research questions in the PICO (Population, Intervention/Indicator, Comparator/Control, Outcome) format (22) (Table 1). Only outcomes of clinical relevance were considered.

Literature Search Methodology

A single strategy was generated using medical subject headings and text words for OSA. A "prognosis" strategy was adapted from McMaster University's filters for prognosis and etiology studies. Comments, editorials, interviews, lectures, letters, and patient education handouts were removed (*see* Table E1 in the online supplement). A "therapy" strategy was developed and covered the following treatments: continuous positive airway, weight loss, oral appliances (OA), and upper airway surgery in Ovid Medline and adapted for execution in Embase, Cochrane Database of Systematic Reviews, Cochrane Central

Table 1. PICO Questions and Inclusion and Exclusion Criteria

PICO Questions

PICO 1. Does mild OSA in comparison to absence of OSA contribute to adverse long-term neurocognitive outcomes, such as daytime sleepiness, poor attention/memory loss, motor vehicle accidents, depression, and poor quality of life?

PICO 2. Does treatment of mild OSA in comparison to no treatment prevent or reduce adverse neurocognitive consequences and motor vehicle accidents and improve quality of life?

PICO 3. Does mild OSA in comparison to the absence of OSA contribute to adverse long-term cardiovascular outcomes, such as hypertension, coronary artery disease, cerebrovascular events, arrhythmias, and cardiovascular and all-cause mortality?

PICO 4. Does treatment of mild OSA in comparison to no treatment prevent or reduce adverse cardiovascular outcomes, including hypertension, coronary artery disease, cerebrovascular events, arrhythmias, and cardiovascular and all-cause mortality?

Inclusion and exclusion criteria for selection of studies

Inclusion criteria

AHI, RDI, or ODI 5–15/h of sleep and pertaining to the 4 PICO questions.

Exclusion criteria

1. Type of publication: reviews, case reports, editorials, letters to the editor without data, only abstract form exists.
2. Subjects other than adults (age $<$ 18 yr).
3. Not OSA (central sleep apnea and hypoventilation syndromes).
4. Intervention is not PAP, weight loss/lifestyle change, oral/dental appliance or surgery, other intervention that is considered to be of value.
5. AHI/RDI/ODI not clearly categorized into 5–15/h or studies that reported results with subjects with mild and moderate OSA combined, absence of comparison with a normal group, or absence of statistical comparison.

In addition, studies that combined mild and moderate OSA and studies without a normal control group were excluded.

Definition of abbreviations: AHI = apnea–hypopnea index; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; PAP = positive airway pressure; PICO = Population, Intervention, Comparator, Outcome; RDI = respiratory disturbance index.

Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment, National Health Service Economic Evaluation Database, PubMed, Directory of Open Access Journals, and PsycINFO.

Literature Review Methodology

Pragmatic systematic reviews were conducted. The prognosis and therapy searches retrieved 4,716 and 3,501 citations, respectively (Figure E1). After the second screen and additional hand searching, 67 and 16 articles were included in the "prognosis" tables (Tables 2 and 4, Tables E3 and E5) and "therapy" tables (Tables 3 and 5, Tables E4 and E6), respectively.

Evidence Syntheses

Question 1: Does Mild OSA in Comparison to Absence of OSA Contribute to Adverse Long-Term Neurocognitive Outcomes, Such as Daytime Sleepiness, Poor Attention/Memory Loss, Motor Vehicle Accidents, and Poor Quality of Life?

Five distinct domains were assessed: daytime sleepiness, motor vehicle accidents (MVAs), quality of life, neurocognitive function, and mood (Table 2, Table E3).

Daytime sleepiness. No longitudinal studies were identified evaluating incident excessive daytime sleepiness (EDS) or worsening sleepiness in those with mild OSA. There were 30 studies (8, 23–51) that reported the cross-sectional association of mild OSA with daytime sleepiness. Two large population-based studies found that the Epworth Sleepiness Scale (ESS) score was slightly higher in persons with mild OSA. In the SHHS (Sleep Heart Health Study) (25), the ESS score in those with respiratory disturbance index (RDI) less than 1.5 and 1.5 to less than 5 were 7.1 and 7.5 respectively, in comparison to 7.8 in those with RDI 5 to less than 15. In the MrOS (Osteoporotic Fractures in Men) study (28), the ESS score was 5.9 in those with AHI less than 7.9/h versus 6.0/h in those with AHI 7.9/h to less than 18.9/h. In three smaller population-based studies (27, 40, 45), two observed that the ESS score was higher in those with mild OSA (27, 45). The third found the prevalence of EDS was similar in those with mild OSA (36%) versus no OSA (37%) (40). A clinic-based study reported that individuals with mild OSA were not more likely to report sleepiness than no OSA (odds ratio [OR], 1.37; 95% confidence interval [CI], 0.6–3.3) (8). In the APPLES (Apnea Positive Pressure Long-term Efficacy Study), there was no relationship in baseline level of sleepiness in either multivariate correlation analysis (26) or a specific comparison between participants with no OSA (ESS, 9.8 ± 3.5) and mild OSA (ESS, 10.6 ± 4.3) (47). The impact of mild OSA on sleepiness in a number of smaller studies was discordant. Furthermore, studies have not evaluated sex and racial differences in the impact of mild OSA on sleepiness.

In summary, most medium to large population-based cross-sectional studies suggest mild OSA is associated with approximately a 0.5-point increase in mean ESS score, the clinical relevance of which is unclear. Studies derived from clinic populations were discordant. Longitudinal data are lacking to demonstrate whether mild OSA is associated with new or worsening daytime sleepiness.

MVAs. There are limited data regarding the risk of MVAs in patients with mild OSA. In a longitudinal population-based study, the risk for any MVA over a period of 5 years was significantly increased in men (OR, 4.2; 95% CI, 1.6–11.3) but not in women (52). In 161 truckers, 34.8% of whom had mild OSA, there was no relationship between OSA severity and crash risk (45). In a case-control study, those with mild OSA had an increased relative risk (RR) of an MVA (RR, 2.6; 95% CI, 1.7–3.9) (53). A metaanalysis (54) found a nonsignificant trend for OSA severity as a risk factor for MVA. Two

Table 2. Studies Pertinent to the Question, Does Mild Obstructive Sleep Apnea in Comparison to Absence of Obstructive Sleep Apnea Contribute to Adverse Long-Term Neurocognitive Outcomes, Such as Daytime Sleepiness, Poor Attention/Memory Loss, Motor Vehicle Accidents, and Poor Quality of Life?

Studies	Participants with Mild OSA	Major Results*
Daytime sleepiness		
30 cross-sectional studies	Mean age ranged from 38 to 82 yr	In 20 studies comparing mild OSA with no OSA, there were no significant differences in self-reported sleepiness, the ESS, the SSS, or the risk of sleepiness (8, 23, 26, 29, 33–44, 46, 47, 51, 53). In 9 studies comparing mild OSA with no OSA, the ESS was greater in the mild OSA group or there was an association between the AHI and ESS (24, 27, 28, 30, 31, 45, 48–50). In 1 study, no specific comparison between mild OSA and no OSA was performed (25).
MVA		
5 cross-sectional	Mean age ranged from 45 to 50 yr	In 2 studies, there was no relationship between severity of sleep-disordered breathing and accident risk or crash rate (45, 56). In 3 studies comparing mild OSA with no OSA, the MVA risk was increased among individuals with mild OSA (53, 55, 98).
Quality of life		
5 cross-sectional studies	Mean age ranged from 41 to 82 yr	In 4 studies comparing mild OSA with no OSA, mild OSA was not associated with the FOSQ in 2 studies (27, 28) or the SAQLI (33, 47) in 2 studies. However, in 1 study, there was a reduction in vitality on the SF-36 (57).
Neurocognitive function		
3 cross-sectional studies	Mean age ranged from 46 to 61 yr	In 3 studies comparing mild OSA with no OSA, there were no differences in PVT scores (58) or a battery of neurocognitive test scores (26, 59).
Mood		
5 cross-sectional studies	Mean age ranged from 47 to 53 yr	In 1 study, there was an association between mild OSA and depression measured by the Zung Depression Scale (60). In 4 studies comparing mild OSA with snoring alone or no OSA, there were no significant differences in mood as measured by various depression scales (BDI, HAM-D, POMS, depression subscales of Psychological General Well-Being Index) (32, 33, 47, 51).

Definition of abbreviations: AHI = apnea–hypopnea index; BDI = Beck Depression Inventory; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; HAM-D = Hamilton Depression Rating Scale; MVA = motor vehicle accident; OSA = obstructive sleep apnea; POMS = Profile of Mood States; PVT = Psychomotor Vigilance Testing; SAQLI = Sleep Apnea Quality of Life Index; SF-36 = Short Form Medical Outcomes Survey; SSS = Stanford Sleepiness Scale.
**See* online supplement for details.

other studies from clinic populations report conflicting results for those with mild OSA (55, 56).

In summary, a limited number of population-based and clinic-based studies provide conflicting data regarding the risk of MVAs associated with mild OSA.

Quality of life. Three large population-based cross-sectional studies evaluating the impact of mild OSA on quality of life were identified. One study in elderly men and another in elderly women failed to show any association between mild OSA and the Functional Outcomes of Sleep Questionnaire (FOSQ) score (27, 28). However, the SHHS noted a reduction in the vitality component of the Short Form Medical Outcomes Survey (SF-36) with mild OSA (OR, 1.2; 95% CI, 1.02–1.43 vs. AHI $<$ 5/h) (57). Two other studies (33, 47) did not find an adverse impact on the Sleep Apnea Quality-of-Life Index.

In summary, there are few studies that have evaluated the impact of mild OSA on quality of life with conflicting results from population-based studies.

Neurocognition. No large population-based studies have examined the relationship between mild OSA and neurocognitive function. However, in the APPLES trial, there was no baseline correlation between AHI severity and any of the large number of neurocognitive tests performed (26). Two other studies also found no association of mild OSA and neurocognitive function (58, 59).

In summary, the absence of large population-based studies constrains the ability to provide an evaluation of the relationship between mild OSA and neurocognition. The limited clinic-based data do not provide any evidence of an association between mild OSA and neurocognitive function.

Mood. Mixed longitudinal/cross-sectional analyses of the population-based Wisconsin Sleep Cohort found an association between mild OSA and depression (OR, 2.0; 95% CI, 1.4–2.9) (60). Three other cross-sectional studies examined the association of mild OSA with mood (32, 33, 47) using a variety of different depression scales. None found any association between assessments of either depression or anxiety with mild OSA.

In summary, there are limited data examining the association between mild

Table 3. Studies Pertinent to the Question, Does Treatment of Mild Obstructive Sleep Apnea in Comparison to No Treatment Prevent or Reduce Adverse Neurocognitive Consequences and Motor Vehicle Accidents and Improve Quality of Life?

Studies	Participants with Mild OSA	Major Results*
Effect of therapy on daytime sleepiness		
6 randomized controlled trials	Mean age ranged from 44 to 52 yr	In 1 RCT comparing intervention with CPAP vs. placebo pill, there was a significant decrease in the ESS in relation to baseline values at 3 wk (63). In 1 RCT comparing CPAP vs. oral appliance vs. placebo tablet, there was a significant decline in the ESS with each active intervention at 3 mo (62), but there were no changes in objective measures of sleepiness using MSLT/MWT (62, 63). In 2 RCTs comparing CPAP vs. placebo pill and active vs. sham CPAP, there was no significant change in the ESS scores at 4 wk (64) or at 6 mo (66), respectively. In 1 study comparing radiofrequency surgery vs. sham, there was no change in the ESS at 4–6 mo (71), and in another, there was no improvement in the ESS scores after 1 yr of successful weight loss with diet and lifestyle modification (68).
4 nonrandomized interventional studies without control and 1 retrospective study	Mean age in mild OSA groups ranged from 41 to 52 yr	In 3 studies, there was a significant decline in ESS with CPAP (61), oral appliance (67), and upper airway surgery (70). In 1 study, there was no change in ESS after intervention with oral appliance (65).
Effect of therapy on quality of life		
5 randomized controlled trials, 1 nonrandomized study without control	Mean age in mild OSA groups ranged from 44 to 52 yr	In 1 RCT, there were no significant differences in GHQ-28 and NHP Part 2 scores between CPAP vs. placebo pill (64). In another RCT, there was no significant difference in the SF-36 scores between radiofrequency surgery of soft palate and placebo applicator (71). However, in 3 RCTs, the SF-36 scores improved in a few domains with CPAP vs. placebo (62, 63), with oral appliance vs. placebo (62), the FOSQ improved with CPAP vs. placebo (62), and the 15D questionnaire improved with very low calorie diet + lifestyle modification vs. lifestyle modification alone (68). In 1 nonrandomized study, the SAQLI improved with CPAP (61).
Effect of therapy on neurocognitive function and mood		
4 randomized controlled trials	Mean age ranged from 44 to 52 yr	In 2 RCTs, there were no significant differences with CPAP vs. sham-CPAP or oral appliance vs. placebo on majority of neurocognitive tests (62, 66). In 2 RCTs, there was improvement in the Trail Making B, Digit Symbol Substitution Task, PASAT-2 testing, and the HADS depression scores with CPAP vs. placebo (63, 64).

Definition of abbreviations: CPAP = continuous positive airway pressure; ENT = ear-nose-throat; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; GHQ-28 = General Health Questionnaire-28; HADS = Hospital Anxiety and Depression Scale; MSLT = Mean Sleep Latency Test; MWT = Maintenance of Wakefulness Test; NHP = Nottingham Health Profile; OSA = obstructive sleep apnea; PASAT = Paced Auditory Serial Addition Test; RCT = randomized controlled trial; SAQLI = Sleep Apnea Quality of Life Index; SF-36 = Short Form Medical Outcomes Survey.
**See* online supplement for details.

OSA and mood. One large population-based study found an association, but concurrence was not found in three smaller primarily clinic-based studies.

Question 2: Does Treatment of Mild OSA in Comparison to No Treatment Prevent or Reduce Adverse Neurocognitive Consequences and MVAs and Improve Quality of Life?

Studies reported on the effect of therapy on daytime sleepiness, quality of life, neurocognition, and mood (Table 3, Table E4). Adherence to continuous positive airway pressure (CPAP) therapy was overall modest.

Daytime sleepiness. Eleven studies (61–71) reported on the effect of therapy on EDS. Four randomized controlled trials (RCTs) (62–64, 66) and four observational studies (61, 65, 67, 70) assessed the effect of CPAP; one RCT (62) and two observational studies (65, 67) assessed the effect of OA; one RCT (71) and one observational study assessed the effect of upper airway surgery (70), and one RCT evaluated the impact of a weight loss/lifestyle intervention (68). All papers on OA used mandibular advancement splints/devices. Efficacy of the intervention was demonstrated in all studies, with significant improvement in OSA severity in all but one study (71).

In a small placebo-controlled RCT (64), no differences were observed in sleepiness between CPAP and a placebo pill at 1 month by either subjective (ESS [mean ± SE]: CPAP, 10.1 ± 1.4 vs. placebo, 10.0 ± 1.2) or objective measures (Multiple Sleep Latency Test: CPAP, 10 ± 1.2 vs. placebo 9.9 ± 1.5 min). A subsequent study by the same group (63) with more symptomatic patients, found improvement in ESS

(CPAP, 8 ± 4 vs. placebo, 11 ± 4) but not objective sleepiness (Maintenance of Wakefulness Testing: CPAP, 16.2 ± 10.6 vs. placebo 14.4 ± 8.5 min) after 4 weeks of CPAP compared with oral placebo. In an RCT, the effects of CPAP, OA, and a placebo tablet on sleepiness were evaluated in subjects with mild to moderate OSA (62). In a planned *post hoc* analysis of data in those with mild OSA, both CPAP and OA were significantly better than placebo in improving the ESS (data not shown).

In contrast, the large APPLES RCT (66) found no differences in subjective (ESS: CPAP, 8.37 ± 4.64 vs. sham CPAP, 7.64 ± 3.98) or objective sleepiness (Maintenance of Wakefulness Testing: CPAP, 17.77 ± 4.00 vs. sham CPAP, 17.89 ± 3.27 min) between active CPAP and sham CPAP at 6 months in participants with mild OSA. Other small RCTs did not demonstrate an improvement in the ESS scores after surgery (71) or weight loss (68), but observational studies noted improvements in ESS with CPAP (61), OA (67), and surgery (70).

In summary, most randomized controlled studies with CPAP demonstrate that treatment of mild OSA improves subjective assessments of daytime sleepiness by a small amount but that this effect may only be present in patients with an elevated level of sleepiness at baseline. However, limited existing data show no impact of treatment on objective assessments of sleepiness. The impact of non-PAP therapies on daytime sleepiness remains unclear.

Quality of life. Only a small number of studies, including five RCTs (62–64, 68, 71), have assessed the impact of mild OSA on quality of life. In one RCT, significant improvement was observed in many but not all quality-of-life measures after 4 weeks of CPAP compared with placebo (63). However, an earlier smaller RCT by the same group did not find significant effects on quality of life (Nottingham Health Profile: CPAP, 1.4 ± 0.6 vs. placebo, 3.2 ± 1.3) (64). Another RCT (62) also found that both CPAP and OA improved the FOSQ (change in CPAP, 0.07; change in OA, 0.06) and CPAP increased three SF-36 subscales (change in vitality subscale, 12.8; change in social functioning subscale, 10.1; and change in mental health subscale, 6.4) compared with placebo. Three small studies demonstrated discordant results, with improvement after CPAP (61) and weight loss (68) but not surgery (71).

In summary, most studies seem to show a small improvement in quality of life caused by treatment of OSA. However, the effect does not seem to be observable in exactly the same quality-of-life domains each time.

Neurocognition. Four RCTs provide evidence in this category (62–64, 66). Improvements with CPAP were seen after 1 month in two out of seven cognitive tasks compared with an oral placebo (63) in one study; however, in an earlier study by the same authors (64) improvement was observed only in the Trail Making Task B in subjects with good CPAP adherence (placebo, 76.1 ± 14.1 s vs. CPAP, 61.9 ± 9.1 s). In one RCT (62), improvements in several neuropsychological outcomes on CPAP and oral appliance were noted in a subset of subjects with mild OSA but not in another RCT comparing CPAP to sham CPAP (66). No studies have evaluated the impact of therapy for mild OSA in a population with cognitive deficits at baseline.

In summary, clinical trials are not consistent on which measures of neurocognitive function, if any, improve as a result of treatment for mild OSA.

Mood. Two small RCTs (63, 64) showed significant improvement in the depression component of the Hospital Anxiety and Depression Scale after 1 month of CPAP compared with placebo (placebo, 5.0 + 1.0 vs. CPAP, 3.4 + 0.9 [64] and placebo, 5.7 ± 3.9 vs. CPAP, 4.0 ± 3.0 [63], respectively) but not in the Hospital Anxiety and Depression Scale anxiety score (placebo, 5.1 ± 1.1 vs. CPAP, 4.5 ± 1.2 [64] and placebo, 6.5 ± 3.8 vs. CPAP, 5.6 ± 3.0 [63], respectively). These results have not been replicated in larger populations.

In summary, there are limited data regarding the effect of treatment of mild OSA on mood, limiting our ability to determine whether mood improves after treatment.

There were no data with respect to the treatment of mild OSA and its impact on MVA.

Question 3: Does Mild OSA in Comparison to the Absence of OSA Contribute to Adverse Long-Term Cardiovascular Outcomes, Such as Hypertension, Coronary Artery Disease, Cerebrovascular Events, Arrhythmias, and Cardiovascular and All-Cause Mortality?

Cardiovascular outcomes including hypertension, cardiac and cerebrovascular events, arrhythmias, and mortality were assessed (Table 4, Table E5).

Hypertension. Three longitudinal studies evaluated population-based cohorts (72–74) and one evaluated a clinic-based cohort (75). An analysis of the Wisconsin Sleep Cohort found that mild OSA was associated with an elevated risk of hypertension (72) at 4 years of follow-up after adjusting for baseline hypertension status (OR, 2.03; 95% CI, 1.29–3.19). In addition, over 7.2 years of follow-up, there was an increased risk of incident nondipping systolic blood pressure (BP) (OR, 3.1; 95% CI, 1.3–7.7) (76).

However, the SHHS performed a 5.2-year follow-up of nonhypertensive individuals (73) and found that after adjusting for age, sex, race, and body mass index (BMI), the OR for incident hypertension in those with mild OSA was not statistically increased (OR, 0.94; 95% CI, 0.73–1.22). Similarly, in the Vittoria Sleep Cohort, the OR for incident hypertension was not elevated after adjusting for multiple confounders, including age, sex, and BMI (OR, 0.90; 95% CI, 0.61–1.34) (74). In the Zaragoza Sleep Cohort (75) it was unclear if those with mild OSA were at elevated risk, as separate results for mild OSA are not reported.

At least five population-based cross-sectional analyses of mild OSA and hypertension have been conducted (24, 77–80). After adjustment for important confounders, such as age, sex, and obesity, the associations between these two conditions were not statistically significant in all but one study (77).

In summary, current data do not indicate that important differences in hypertension risk exist among those with mild OSA when stratified by age, sex, BMI, or baseline level of sleepiness. Although longitudinal studies found that elevated crude associations exist between hypertension and mild OSA, the studies were conflicting on whether the elevated risk can be explained by differences in important confounders such as age, sex, and BMI. Cross-sectional analyses provide conflicting results.

Cardiovascular events. Evidence exploring the association of mild OSA and cardiovascular events is derived from four prospective cohorts and a few cross-sectional studies. The Wisconsin Cohort Study found that after 24 years of follow-up,

Table 4. Studies Pertinent to the Question, Does Mild Obstructive Sleep Apnea in Comparison to the Absence of Obstructive Sleep Apnea Contribute to Adverse Long-Term Cardiovascular Outcomes Such as Hypertension, Coronary Artery Disease, Cerebrovascular Events, Arrhythmias, and Cardiovascular and All-Cause Mortality?

Studies	Participants with Mild OSA	Major Results*
Hypertension		
5 prospective observational cohort analyses and 18 cross-sectional studies	Mean age ranged from 44 to 67 yr	Five prospective cohort studies: In 3 studies, there appeared to be no increase in the odds for incident hypertension in subjects with mild OSA vs. control subjects (73–75), whereas in 1 cohort, the risk for incident hypertension was significantly increased in subjects with mild OSA vs. control subjects (72) with increased nondipping of BP with mild OSA (76). Eighteen cross-sectional studies: After adjusting for multiple confounders, there was an increased risk for hypertension or elevated BP in 1 population-based study (77). There was an increased percent of individuals with high BP in mild vs. no OSA groups in another study (80). However, there was no increase in the risk for elevated BP or hypertension, after adjusting for confounders, in the remaining cross-sectional studies (8, 24, 46, 78, 79, 99–101) where BP was the primary outcome, nor was there an increased risk in 9 additional studies (36, 37, 41, 42, 49, 90, 102, 103) where BP was not the primary outcome.
CAD and CHF		
4 prospective observational cohort studies and 5 cross-sectional studies	Mean age in mild OSA groups ranged from 50 to 67 yr/older adults	In 2 prospective observational cohort studies, there was no increase in the risk for CAD or CHF in mild OSA vs. no OSA after 8 yr of follow-up (83) or in cardiovascular events after a 20-yr follow-up (84). However, in 2 prospective cohort studies, the risk of combined CAD and CHF was increased in mild OSA vs. no OSA after 24 yr of follow-up (81) or was independently associated with coronary events during a 2.9-yr follow-up (82). In 5 cross-sectional analyses, there were no significant differences in the percentages of patients with CAD/CHF or risk for CAD/CHF in mild OSA vs. no OSA (37, 41, 42, 88, 90).
Combined cardiovascular endpoints		
4 prospective observational cohort studies and 1 retrospective analysis of a clinical cohort	Mean age ranged from 50 to 60 yr	In 4 studies, there was no association of mild OSA with a composite endpoint (12, 85, 97, 104). However, in 1 study, mild OSA was independently associated with coronary events or death from cardiovascular causes (combined endpoint) (82).
Cerebrovascular accidents		
4 prospective observational cohort studies and 5 cross-sectional	Mean/median age in mild OSA groups ranged from 50 to 72 yr	In 3 prospective observational cohort studies (12, 84, 86), there were no significant differences in the percentage of patients with stroke or the risk of stroke in mild OSA vs. no OSA. However, in 1 prospective observational cohort study in patients with underlying CAD, there was an increased risk of stroke with mild OSA vs. no OSA (87). In 5 cross-sectional studies (37, 41, 88, 90), there were no significant differences in the percentage of patients with stroke in mild OSA vs. no OSA groups.
Cardiac arrhythmias		
3 cross-sectional analyses	Mean age ranged from 50 to 55 yr	Cross-sectional analysis of a population-based longitudinal study (MrOS Sleep Study) did not find an increased risk for atrial fibrillation or complex ventricular ectopy in patients with mild OSA vs. no OSA (89). In 2 cross-sectional clinic-based studies, there was no association of cardiac arrhythmias with increasing severity of OSA (90) and no significant difference in the percentage of patients with atrial fibrillation in the mild OSA vs. no OSA groups (37).
Cardiovascular and all-cause mortality		
Cardiovascular mortality: 2 prospective observational cohort studies	Mean age ranged from 50 to 56 yr	In both studies, there was no increase in the risk for cardiovascular mortality in patients with mild OSA vs. no OSA (91, 93).
All-cause mortality: 5 prospective observational cohort studies	Mean age ranged from 50 to 65 yr	In all 5 studies, there was no increase in all-cause mortality in patients with mild OSA vs. no OSA (84, 91–93, 105).

Definition of abbreviations: BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; MrOS = Osteoporotic Fractures in Men; OSA = obstructive sleep apnea.
**See* online supplement for details.

there was an increased risk of combined coronary artery disease (CAD) and heart failure events among patients with mild OSA compared with patients with no OSA (adjusted hazard ratio [HR], 1.9; 95% CI, 1.05–3.5) after excluding patients on CPAP (81). In a sleep clinic–based cohort (82), mild OSA was independently associated with coronary events or death from cardiovascular causes during a 2.9-year follow-up (OR, 2.22; 95% CI, 1.10–4.45). In contrast, in the SHHS, the HR was nonsignificant for incident CAD (HR for men, 0.91; 95% CI, 0.69–1.20; HR for women, 0.98; 95% CI, 0.69–1.38) and heart failure (HR for men, 0.88; 95% CI, 0.57–1.35; HR for women, 1.13; 95 % CI, 0.80–1.61) assessed over 8.7 years (83). The Busselton cohort also noted that mild OSA was not associated with cardiovascular events after a 20-year follow-up (HR, 1.0; 95% CI, 0.60–1.7) (84). Retrospective analysis of a large sleep clinic cohort showed no association of mild OSA with different composite outcomes that included myocardial infarction, stroke, heart failure, revascularization procedures, or death from any cause (85).

In summary, there is conflicting evidence from longitudinal population-based studies making it unclear whether there is an association between mild OSA and increased incidence of cardiovascular events.

Cerebrovascular events. Three longitudinal studies failed to demonstrate an association between mild OSA and stroke (12, 84, 86). A conflicting report (87) in patients with CAD showed that mild OSA was an independent risk factor for incident stroke (OR, 2.44; 95% CI, 1.08–5.52) after 10 years of follow-up in patients with CAD referred for coronary angiography. In the population-based SHHS, after covariate adjustment, there was no increase in stroke risk in the second quartile (AHI, 4.05/h to <9.5/h) in comparison to the first quartile (AHI < 4.0/h) of the AHI distribution for both men and women (HR for men, 1.86; 95% CI, 0.67–5.12; HR for women, 1.34; 95% CI, 0.76–2.36) (86). Additionally, the population-based Busselton cohort study reported that mild OSA was not independently associated with incident stroke after a 20-year follow-up period (HR, 1.0; 95% CI, 0.39–2.7) (84). In a clinic-based study, the risk for the combined endpoint of stroke or death in individuals with mild OSA (defined as AHI 4/h–12/h) was not significantly elevated compared with those with AHI less than 4/h (HR, 1.75; 95% CI, 0.88–3.49) (12).

Cross-sectional analyses of a large population-based cohort (88) did not find differences in the percentage of patients

Table 5. Studies Pertinent to the Question, Does Treatment of Mild Obstructive Sleep Apnea in Comparison to No Treatment Prevent or Reduce Adverse Cardiovascular Outcomes, Including Hypertension, Coronary Artery Disease, Cerebrovascular Events, Arrhythmias, and Cardiovascular and All-Cause Mortality?

Studies	Participants with Mild OSA	Major Results*
Effect of therapy on hypertension		
1 RCT with 3 publications, 1 nonrandomized intervention study, 1 prospective cohort observational study, 1 retrospective cohort study	Mean age ranged from 45 to 51 yr	In 1 RCT, there was no significant change in the systolic and diastolic BP after successful weight loss with diet + lifestyle modifications (68) vs. conventional care at 1 yr. Subsequent follow-up at 2 and 5 yr (69, 94) did not find significant changes in systolic or diastolic BP between the two groups. However, the antihypertensive medications were discontinued in 39% of participants in the intervention group vs. 14% in the control group (69). In 1 retrospective cohort (96) with normal BP at baseline and 1 nonrandomized intervention study (95), there was a significant decrease in the mean arterial BP with CPAP vs. no CPAP therapy (96) and a decline in the mean 24-h systolic or diastolic BP with evidence of dipping (95) after upper airway surgery vs. before surgery or in comparison to the no OSA group, respectively. In a prospective observational cohort (75), there were no significant differences ($P = 0.15$) in the risk of developing hypertension among patients who were ineligible for CPAP (n = 255; CIR, 3.02; 95% CI, 2.43–3.61), declined CPAP therapy (n = 11; CIR, 2.88; 95% CI, 0.10–5.66), were nonadherent (n = 11; CIR, 4.05; 95% CI, 0.57–7.53), or were on active CPAP therapy (n = 57; CIR, 2.12; 95% CI, 1.02–3.22).
Effect of therapy on all-cause mortality		
1 retrospective cohort study	Mean age, 50 yr	In this study comparing treatment with CPAP vs. untreated with CPAP owing to refusal or <4 h of therapy per night, there was no significant difference in all-cause mortality in the treated vs. untreated groups (97). There were no studies pertaining to the impact of therapy on cardiovascular mortality.

Definition of abbreviations: BP = blood pressure; CI = confidence interval; CIR = crude incidence rate per 100 person-years; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; RCT = randomized controlled trial.
**See* online supplement for details.

with stroke in mild-OSA versus no-OSA groups.

In summary, mild OSA is not associated with an increase in CVA events in subjects from the general population or patients referred for sleep studies. However, limited data suggest that mild OSA may increase stroke risk in persons with underlying CAD.

Arrhythmias. No longitudinal studies have addressed the impact of mild OSA on arrhythmias. Cross-sectional analysis of one population-based study (MrOS Sleep Study) did not find an increased risk for atrial fibrillation or complex ventricular ectopy in patients with mild OSA versus no OSA (89). Two clinic-based cross-sectional analyses found no association of atrial fibrillation (37) or other arrhythmias (90) with mild OSA.

In summary, there are limited data available to assess the association of mild OSA to risk of atrial fibrillation or other arrhythmias.

Cardiovascular and all-cause mortality. In the 18-year follow-up of the Wisconsin Cohort Study, mild OSA was not associated with increased cardiovascular mortality (HR, 1.8; 95% CI, 0.7–4.9) (91). With respect to all-cause mortality, five population-based studies with 8 to 20 years of follow-up and a sleep clinic study found no increase with mild OSA (84, 91–93, 105).

In summary, compared with subjects without OSA, available evidence from population-based longitudinal studies indicates that mild OSA is not associated with increased cardiovascular or all-cause mortality.

Question 4: Does Treatment of Mild OSA in Comparison to No Treatment Prevent or Reduce Adverse Cardiovascular Outcomes, Including Hypertension, CAD, Cerebrovascular Events, Arrhythmias, and Cardiovascular and All-Cause Mortality?

Available studies only reported on the effect of therapy on hypertension and mortality (Table 5, Table E6).

Hypertension. In one RCT, patients with mild OSA were randomized to either an intensive lifestyle intervention or a control arm and followed over 1 year (68). Participants were followed over 5 years in two subsequent publications (69, 94). Participants in the intervention group lost more weight than the control group and had a greater resolution of OSA. No

Table 6. Knowledge Gaps

Neurocognitive outcomes

1. There exists a gap in understanding which modifiable and nonmodifiable factors determine individual susceptibility to develop sleepiness from mild OSA.
2. There is a discrepancy between the effect of treating mild OSA on subjective sleepiness and its impact on objective assessment of sleepiness. There is a gap in understanding the source of this discrepancy.
3. The risk for MVA related to mild OSA is understudied. In addition, whether treatment of mild OSA has any beneficial impact on the risk for MVA remains unclear.
4. The impact of mild OSA on quality of life is uncertain. A limited number of population-based studies have provided contradictory results. It is also not clear which domains of quality-of-life measurements are most sensitive to mild OSA and in which specific subgroups of patients.
5. There is a paucity of prospective observational studies that have assessed the effect of mild OSA on neurocognitive function in the elderly or populations that may plausibly be at a higher risk for developing accelerated neurocognitive deficits. Moreover, the results are inconsistent on which measures of neurocognition, if any, improve after treatment of mild OSA in subgroups with underlying neurocognitive deficits.
6. One longitudinal cohort observed a negative impact of mild OSA on mood. This finding requires confirmation. Moreover, there are very limited data regarding the effect of treatment of mild OSA on mood.
7. There are limited or no data regarding whether age, sex, race, or ethnicity modify the impact of mild OSA on daytime sleepiness, quality of life, neurocognitive function, and mood, and treatment thereof.

Cardiovascular outcomes

1. It is unclear whether mild OSA plays a causal role in elevating blood pressure or increasing the risk of incident hypertension.
2. There is a lack of large-scale randomized controlled trials examining the impact of PAP therapy on existing hypertension in patients with mild OSA.
3. A few longitudinal studies have made direct comparisons of the risk of incident stroke and coronary heart disease between mild OSA and normal groups, and the results are contradictory.
4. There are no prospective observational studies that have focused on determining whether an association exists between mild OSA and the risk for developing atrial fibrillation and other arrhythmias.
5. It is unclear whether there is a differential impact of mild OSA on hypertension and cardiovascular complications in high-risk populations (e.g., individuals with underlying cardiovascular disease or multiple comorbid conditions) as well as those who are sleepy.
6. It is not known whether race or ethnicity modifies the impact of mild OSA on specific cardiovascular outcomes and treatment thereof.

Other

1. There is an absence of data on the relative impact of the differing definitions of hypopnea on the assessment of neurocognitive and cardiovascular outcomes in mild OSA vs. no OSA.
2. There are limited studies on the impact of non-PAP therapies, including oral appliances, surgery, or weight loss, alone or in combination, on different neurocognitive and cardiovascular outcomes.
3. There were no studies that investigated whether there was an association between mild OSA characterized by REM sleep predominance and neurocognitive and/or cardiac outcomes or whether treatment of this condition improves these outcomes.
4. Many studies had insufficient number of measurable events preventing accurate estimation of outcomes.

Definition of abbreviations: MVA = motor vehicle accidents; OSA = obstructive sleep apnea; PAP = positive airway pressure.
For the sake of clarity, the knowledge gaps were grouped into separate categories.

significant changes in BP were seen at 12 months. However, 5 of 18 patients (28%) in the intervention group discontinued drug treatment for hypertension, compared with 2 of 15 (13%) in the control group. At 2 years (69), 20 of 35 (57%) of the intervention group compared with 11 of 36 (31%) of the control group no longer had OSA (similar to the 1-year findings), and 7 of 18 participants (39%) in the intervention group had their antihypertensive medications discontinued compared with only 2 of 14 (14%) in the control group. At 5-year follow-up (94), 10 of 20 (50%) of the intervention group compared with 4 of 37 (11%) of the control group no longer had OSA, but there were no changes in systolic or diastolic BP.

One prospective study (75) found no significant difference in the risk of developing hypertension among patients with mild OSA who were ineligible for CPAP, declined CPAP therapy, were nonadherent, or were on active CPAP therapy. In a study without a control arm, patients with hypertension and OSA underwent nonstandardized surgical treatment for their OSA (95). In those with mild OSA, improvements in mean 24-hour systolic, daytime systolic, and diastolic and nocturnal systolic BP were observed on follow-up. Furthermore, a significant conversion to dipping status was seen in participants with mild OSA with hypertension compared with those with hypertension alone (51.7 vs. 31.9%, respectively). In a retrospective longitudinal study of normotensive patients with mild OSA without preexisting cardiovascular disease, diabetes, or hyperlipidemia followed for 2 years (96), a decrease in mean BP of approximately 2 mm Hg was seen in patients with OSA treated with CPAP. In contrast, an increase in mean BP by approximately 10 mm Hg over 2 years was seen in untreated OSA participants.

Table 7. Research Recommendations

Task Force Recommendations That Will Provide a Clear Framework and Impetus for Well-designed Research Studies Using Rigorous Methodologies and Strategies
1. Standard definitions of mild OSA should be used by the research community to allow comparison of data across the studies. This includes standardization of measurement techniques and categorization of what constitutes an abnormal respiratory event.
2. Measures other than the AHI should be explored as markers for mild OSA.
3. *Post hoc* analyses of existing observational longitudinal studies or randomized trials in treated and untreated participants with mild OSA should be performed to evaluate the impact of treatment of mild OSA on neurocognitive and cardiovascular outcomes.
4. Analyses that combine patient data from ongoing large cohort studies that used comparable methods of event ascertainment should be performed to determine if there is an association of mild OSA with neurocognitive and cardiovascular outcomes.
5. Adequately powered RCTs should be performed in individuals with mild OSA to compare the effectiveness of treatments such as PAP, oral appliances, and weight loss, alone or in combination, to reduce daytime sleepiness. The studies should also clarify the etiology of discrepant results noted in subjective and objective measures of sleepiness.
6. High-quality prospective observational studies are required to determine whether mild OSA increases the risk for motor vehicle accidents and whether patients receiving adequate therapy for mild OSA have lower event rates compared with individuals with no or inadequate therapy
7. High-quality prospective observational studies are required to clarify whether an association exists between mild OSA and the risk for developing neurocognitive deficits and mood disorders.
8. Adequately powered RCTs should be performed in individuals with mild OSA to determine the impact of different OSA therapeutic interventions, including PAP, oral appliances, and weight loss, alone or in combination, on prevalent hypertension.
9. High-quality prospective observational studies are required in patients with mild OSA to fully clarify the risk for developing incident stroke, CAD, heart failure, atrial fibrillation, and other arrhythmias and to inspect the impact of different OSA therapeutic interventions vs. no therapy on these outcomes.
10. Studies should incorporate specific at-risk population groups, including:
a. Cohorts with mild cognitive dysfunction (either with or without sleepiness) to determine the impact of mild OSA on cognition in this high-risk population;
b. Sleepy and nonsleepy cohorts to determine whether any impact of mild OSA on cardiovascular events (e.g., myocardial infarction, stroke, etc.) differentially impacts individuals with sleepiness;
c. Cohorts of motor vehicle operators to ascertain the impact of mild OSA on the frequency of motor vehicle accidents and whether treatment can mitigate any negative consequences;
d. Cohorts with comorbid cardiovascular conditions to determine the impact of mild OSA on cardiovascular events in this high-risk population.
11. Future large-scale studies should incorporate the following characteristics:
a. Include comparisons with a control arm to rule out a placebo effect;
b. Aim to incorporate different age groups, sexes, and races/ethnicities to allow determination whether certain groups are more susceptible;
c. For neurocognitive outcomes, choose from a standard battery of neuropsychometric testing;
d. For hypertension outcomes, use standardized approaches to BP measurement.

Definition of abbreviations: AHI = apnea–hypopnea index; BP = blood pressure; CAD = coronary artery disease; OSA = obstructive sleep apnea; PAP = positive airway pressure; RCT = randomized controlled trial.

In summary, there are no randomized controlled trials in persons with mild OSA where it can be determined whether hypertension can be alleviated or avoided via CPAP, OA, or surgery. Weight loss may be an effective treatment for hypertension, but it is unclear whether this intervention acts solely through effects on OSA. Observational cohorts provide conflicting assessments of the effect of mild OSA treatment on hypertension.

Mortality. There was only one retrospective cohort study identified that reported the effects of CPAP on all-cause mortality in patients with mild OSA (97). Patients with mild OSA who used CPAP more than 4 hours per night did not have lower mortality than less-adherent patients with mild OSA (HR, 1.61; 95% CI, 0.48–5.44). Cardiovascular-specific mortality was not provided in this analysis.

In summary, there was only one observational study on the effects of treatment of mild OSA on fatal and nonfatal cardiovascular events. There was no evidence from this single study that treatment of mild OSA reduces all-cause mortality. There are no studies assessing the impact of treatment on cardiovascular mortality.

There were no studies studying the impact of treatment of mild OSA on stroke, cardiovascular events, atrial fibrillation, or other arrhythmias.

Knowledge Gaps

Our detailed and comprehensive appraisal of the literature revealed multiple research gaps, as described in Table 6.

Research Recommendations

The Task Force developed recommendations to provide a framework and impetus for well-designed research studies using rigorous methodologies and strategies, as detailed in Table 7.

Conclusions

There is evidence that patients with mild OSA who demonstrate subjective sleepiness may benefit from treatment of the disorder. There is no evidence of an elevated mortality risk in the general population. However, there is inconclusive evidence regarding the impact of mild OSA on neurocognition, quality of life, mood, BP, and cardiovascular consequences. Moreover, barring a few studies, most did not follow standard definitions, had methodological flaws, and did not carefully distinguish mild from moderate and severe OSA, providing discordant and thereby potentially misleading information. Thus, future research agendas should address these issues as detailed in the document. ■

This official research statement was prepared by an *ad hoc* subcommittee of the ATS Assembly on Sleep and Respiratory Neurobiology.

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