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

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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.

Contents

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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.

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. The *International Classification of Sleep Disorders* (1) defines OSA as the occurrence of predominantly obstructive apneas (cessation of airflow) and hypopneas (reduction in airflow) denoted by either an apnea–hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) of greater than or equal to 15/h or greater than or equal to 5/h accompanied by cardiovascular, neurocognitive, or metabolic consequences. General population-based studies indicate that the prevalence of OSA syndrome defined as 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); if using a criterion of AHI greater than or equal to 5/h alone, the prevalence is much higher, ranging from 8 to 28% in adult men and 3 to 26% in adult women (2–4, 6, 8–12), respectively. Most of these population-based studies have estimated a two- to threefold greater risk for men than women.

Over the years, there have been a number of attempts to standardize the definitions and diagnostic criteria for OSA to provide a uniform framework for comparing results of research investigations as well as to assist in clinical management. In 1997, a group of experts reached a consensus to categorize OSA into three severity groups on the basis of AHI (13):

1. Mild OSA: 5 to $<$15 events/h
2. Moderate OSA: 15 to $<$30 events/h
3. Severe OSA: $\geqslant$30 events/h

The group acknowledged the lack of prospective studies to validate the definitions and considered the thresholds, also known as the "Chicago criteria" (13), as operational definitions. This consensus statement hoped to stimulate further research to identify the optimal approach to quantifying OSA. The data to justify a severity index on the basis of event frequency and the AHI of 5/h as a minimal threshold value were derived from the Wisconsin Sleep Cohort (7, 14) showing an increasing dose-dependent risk of hypertension that was "substantial" at AHI 30/h. The recommended cutoff of 15/h for moderate OSA was based on both expert consensus opinion and clinical research, where mild OSA has frequently been defined as AHI 5/h to less than 15/h. Consequently, the same AHI severity definition was used in this Research Statement.

Notwithstanding the lack of clarity regarding definitions for OSA severity, observational and interventional data suggest that there are negative health effects as a consequence of OSA, such as hypertension, cardiovascular disease, sleepiness, reduced quality of life, and motor vehicle accidents (MVAs). In observational studies, individuals with OSA have an

increased risk of incident and prevalent hypertension (14–17) and cardiovascular disease, including stroke and myocardial infarction (18–20). Moreover, treatment of OSA with positive airway pressure (PAP) appears to improve blood pressure (BP) (21), especially in patients who are sleepy and adherent to PAP therapy (22). Although there is clear evidence linking OSA to adverse cardiovascular and neurocognitive sequelae, the magnitude of negative impact appears to be dependent on the severity of OSA. Prospective cohort studies indicate that patients with an AHI greater than or equal to 30/h have increased risk for all-cause mortality compared to those with an AHI of 5/h to less than 30/h (19, 23, 24). On the other hand, whether mild OSA has a negative impact on health has been a source of controversy (25–27). For example, studies have reported conflicting results for measures of sleepiness, neurobehavioral performance, mood, and quality of life in patients with mild OSA (28–55). Notably, a 2011 Agency for Health Care Research and Quality report (56) remarked on the lack of clarity regarding the effects of mild OSA (AHI 5/h to $<$15/h) on cardiovascular, neurocognitive, and functional outcomes. It is also not clear whether treatment of mild OSA with PAP or alternative modalities improves clinical outcomes.

A significant proportion of the populace has mild OSA. The Wisconsin Sleep Cohort reported the prevalence to be 7.6% in a general population of middle-aged women and 15.6% in middle-aged men (7). In a follow-up report, 21.4% of the cohort had mild OSA (57). However, the prevalence ranges between 17 and 25% in cohorts undergoing evaluation for OSA (28, 29). Thus, given the lack of consensus as to whether mild OSA has negative sequelae and whether treatment of mild OSA improves health, there is an urgent need to provide the American Thoracic Society (ATS) members and other stakeholders with a critical appraisal of the current evidence describing the impact of mild OSA on neurocognitive and cardiovascular clinical outcomes. Consequently, in January 2013 the ATS commissioned the Impact of Mild OSA Task Force to develop a Research Statement that would review available evidence, identify key research gaps, and make important recommendations for future research endeavors related to mild OSA.

Purpose

The overarching goal of this Research Statement is to provide a state-of-the-art review and critical appraisal of the evidence that describes the neurocognitive and cardiovascular sequelae of mild OSA. Only outcomes of clinical relevance were considered. Hence, topics addressing surrogate markers of atherosclerosis, arterial stiffness, heart remodeling, silent brain infarct, and markers of metabolic dysfunction and inflammation were not evaluated.

Thus, the specific goals of the Mild OSA Task Force were as follows:

1. Describe and appraise the evidence regarding whether or not adverse neurocognitive outcomes, including excessive daytime sleepiness (EDS), reduced attention, increased MVAs, depression, and poor quality of life are attributable to mild OSA in adults;
2. Describe and appraise the evidence regarding whether or not treatment of mild OSA in adults is effective at preventing or reducing these adverse neurocognitive outcomes and improving overall quality of life;
3. Describe and appraise the evidence regarding whether or not adverse cardiovascular clinical outcomes are attributable to mild OSA in adults. These outcomes include hypertension, coronary artery disease (CAD), cerebrovascular events, arrhythmias, and cardiovascular and all-cause mortality.
4. Describe and appraise the evidence regarding whether or not therapy of mild OSA in adults is effective at preventing or reducing the risk of these adverse cardiovascular outcomes and all-cause mortality.

This Research Statement is not intended to be a clinical practice guideline; other documents are available that provide specific clinical recommendations for the overall diagnosis and management of OSA.

Methods

An international task force of experienced clinicians and investigators with expertise in sleep epidemiology, clinical trials, systematic reviews, and official document development were assembled for this project.

Questions

To meet our prespecified goals, the following research questions were developed in the PICO (Population, Intervention/Indicator, Comparator/Control, Outcome) format (58):

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, MVAs, depression, and poor quality of life?
2. Does treatment of mild OSA in comparison to no treatment prevent or reduce adverse neurocognitive consequences, including daytime sleepiness, poor attention/memory loss, MVAs, and depression and improve quality of life?
3. Does mild OSA in comparison to the absence of OSA contribute to adverse long-term cardiovascular outcomes, such as hypertension, CAD, cerebrovascular events, arrhythmias, and cardiovascular and all-cause mortality?
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?

Definition of Mild OSA

Before extracting data from peer-reviewed literature, the Mild OSA Task Force members debated the differing definitions of mild OSA at a face-to-face meeting during the 2013 ATS International Conference in Philadelphia. It was clear that complicating the evaluation of the evidence regarding the consequences and treatment of mild OSA was the high degree of clinical uncertainty and inconsistencies that exist in defining what comprises "mild" OSA. This uncertainty was compounded by contrasting study methodologies and disparate ascertainment of outcomes. Moreover, there were marked variances in measurement techniques and definitions of hypopneas.

Although apneas have been clearly identified as cessation of flow lasting for at least 10 seconds, there have been multiple definitions of "hypopnea" over the years (59–64). Therefore, any conclusions about the impact of mild OSA will be influenced by the definition chosen for hypopnea as well as the cutoff for "normal." Because the

published literature uses widely varying definitions, and studies selected for this review all used an AHI range of 5/h to less than 15/h, it is highly likely that some studies of mild OSA included large numbers of potentially "normal" subjects and others included subjects with moderate OSA, thereby explaining some of the inconsistencies in the results (*see* LIMITATIONS for more discussion). Nevertheless, while remaining cognizant of the aforementioned limitations in the current literature, before reviewing and appraising the available literature, the Task Force members arrived at a consensus of using the 1999 Chicago AHI severity criteria for this Research Statement, with a working definition for mild OSA that included AHI, oxygen desaturation index (ODI), or respiratory disturbance index (RDI) ranging from 5/h to less than 15/h (13), irrespective of the parameters used for defining a hypopnea.

The committee was fully aware that reliance on a consensus-driven index of disease severity is fraught with the risk of oversimplification that does not fully characterize disease severity on the basis of symptoms or heritable, molecular, or other parameters. However, given the current state of research, this was the option to which the committee defaulted.

Literature Search Methodology

Health sciences librarians (B.G., P.E.C., and S.L.K.) designed and conducted the main literature searches. Multiple pragmatic systematic reviews were conducted to answer the above PICO questions. A single strategy was generated using medical subject headings and text words for OSA.

The "prognosis" strategy was adapted from McMaster University's filters for prognosis and etiology studies (*see* Table E1 in the online supplement) using EndNote (Thomson Reuters, Philadelphia, PA). The "therapy" strategy covered the following treatments: continuous positive airway pressure (CPAP), weight loss, oral appliances (OAs), and surgery. Results were refined by study type to include randomized controlled trials (RCTs), observational nonrandomized studies, metaanalyses, systematic reviews, and practice guidelines (Table E2).

Comments, editorials, interviews, lectures, letters, and patient education handouts were removed. The panel opted to retain only original studies and trials. Systematic review articles (published within the last 5 yr) and other reviews (published within the last 3 yr) were identified using EndNote and hand searched. Prognosis and therapy strategies were combined with the OSA strategy to produce a list of potentially relevant citations.

Searches were designed in Ovid Medline and adapted for execution in Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment, and National Health Service Economic Evaluation Database. Results were limited to human studies or studies indexed with neither human nor animal, adults or studies indexed with neither adults nor children, and those published in English or containing an English abstract for all publication years. Additional searches were run in PubMed, Directory of Open Access Journals and PsycINFO by a partnering librarian (A.S.).

To supplement the electronic search, members hand-searched journals, conference proceedings, reference lists, and regulatory agency websites. Pearling (hand searching) of references from systematic reviews, guidelines, and metaanalyses was completed for the prior 5 years. Initial database literature searches were done in June and August of 2013, with an update performed on May 15, 2014. Final hand searches were completed in May 2015.

Literature Review Methodology

Reviewers used predetermined inclusion and exclusion criteria and EndNote software to sort all results from the literature search (Figure E1). Studies pertaining to mild OSA, defined as AHI, RDI, or ODI 5/h to 15/h of sleep, and the four PICO questions were included.

The following were excluded: reviews, case reports, editorials, and letters to the editor without data and abstracts. Studies with subjects younger than 18 years and describing central sleep apnea or obesity hypoventilation were also excluded. A two-step screening method was used: the first screen consisted of a title and abstract review, and the second screen entailed review of the full text.

The prognosis search retrieved 4,716 citations, less duplicates. After the first screen, 799 articles met inclusion criteria for full text review. After the second screen and hand searching, 67 articles were included in the final evidence table (Tables 1 and 3, Tables E3 and E5).

The therapy search retrieved 3,501 citations, less duplicates. After the first screen, 963 articles met inclusion criteria for full text review. After the second screen and hand searching, 16 articles were included in the final evidence tables (Tables 2 and 4, Tables E4 and E6).

After careful review, studies that combined mild and moderate OSA or that used "nonstandard" definitions of OSA severity including subjects with moderate OSA generally were excluded. Similarly, prognostic studies without an appropriate control group (i.e., those without OSA) or without a direct comparison to such a control group were excluded. However, a few studies that stratified OSA severity into several groups including mild OSA were included to emphasize specific issues. Several methodological limitations were identified while appraising the studies and are summarized in LIMITATIONS later.

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, MVAs, and Poor Quality of Life?

Summary of Evidence is provided in Table 1 and Table E3. In reviewing evidence to answer this question, it became apparent that there were five distinct domains to be assessed: sleepiness, MVAs, quality of life, neurocognitive function, and mood. Data related to each of these are summarized separately. However, the preponderance of studies focused on sleepiness.

Daytime sleepiness. No longitudinal studies were identified evaluating incident EDS or worsening sleepiness in those with mild OSA. There were 30 studies (8, 28–53, 65–67) that reported the cross-sectional association of mild OSA with daytime sleepiness. The majority of these studies were of subjects recruited from sleep clinics and therefore susceptible to selection bias. Of the population-based studies, the two largest analyses came from the SHHS (Sleep Heart Health Study) (30) and the MrOS (Osteoporotic Fractures in Men) study (33).

Table 1. 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, 28, 31, 34, 41–53, 66–68). 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 (29, 32, 33, 35–39, 65). In one study, no specific comparison between mild OSA and no OSA was performed (30).
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 (65, 72). In 3 studies comparing mild OSA with no OSA, the MVA risk was increased among individuals with mild OSA (68, 71, 125).
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 (32, 33) or the SAQLI (41, 67) in 2 studies. However, in 1 study, there was a reduction in vitality on the SF-36 (54).
Neurocognitive function		
3 cross-sectional	Mean age ranged from 46 to 61 yr	In 3 studies comparing mild OSA with no OSA, there were no differences in PVT scores (55) or a battery of neurocognitive test scores (31, 73).
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 (74). 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) (40, 41, 43, 67).

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.

The SHHS analysis included 1,672 subjects with mild OSA (30). In the SHHS (30), the Epworth Sleepiness Scale (ESS) score in those with RDI less than 1.5 and 1.5 to 5 were 7.1 and 7.5, respectively, in comparison to 7.8 in those with RDI 5 to 15. However, no specific comparison of no OSA to mild OSA was performed. In the MrOS study (33), 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 18.9/h. The MrOS analysis included 1,009 older men with mild OSA (33). Although the mean ESS score was 6.0 in those with AHI 7.9/h to 18.9/h as compared with 5.9 in those with AHI less than 7.9/h, there was no specific comparison between AHI less than 5/h and AHI 5/h to 15/h. Three smaller population-based studies assessed the association of mild OSA with ESS (32, 49, 65). Among older women in the Study of Osteoporotic Fractures that included 178 women with mild OSA, mean ESS was 5.6 in those with AHI 7.06/h to 17.0/h and 5.2 in those with AHI less than 7.06/h (32). Similar to the MrOS study, there was no specific comparison between AHI less than 5/h and AHI 5/h to 15/h. A study of Australian transportation drivers, including 56 with mild OSA, found the mean ESS was 7.4 in those with mild OSA versus 6.8 in those with no OSA, but there was no statistical comparison of mild versus no OSA (65). In a Swedish study of middle-aged women, including 128 with mild OSA, the prevalence of EDS defined as ESS greater than or equal to 10 was similar in those with mild OSA (36%) and no OSA (37%) (49). Although the prevalence rates of EDS and involuntarily falling asleep during the daytime on the basis of specific questions about the frequency of these symptoms were 22 and 12% in those with mild OSA versus 18 and 8% in those with no OSA, these comparisons were not statistically significant. A Japanese study of middle-aged women, including 619 with mild OSA, found the prevalence of EDS on the basis of a single question was 6.7% in those with mild OSA compared with only 3.6% in those without OSA (29). Finally, a Spanish study of middle-aged individuals, including 115 with mild OSA, also used a single question to define EDS and found those with mild OSA were 37% more likely to report sleepiness than those with AHI of 0, although this was not statistically significant (odds ratio [OR], 1.37; 95% confidence interval [CI], 0.6–3.3) (8).

In the APPLES (Apnea Positive Pressure Long-term Efficacy Study) trial, which recruited from both sleep clinics and the general population, there was no

relationship in baseline level of sleepiness in either multivariate correlation analysis (31) or a specific comparison between participants with no OSA (ESS, 9.8 ± 3.5) and mild OSA (ESS, 10.6 ± 4.3) (67). Of the remaining clinical cohorts, some demonstrated an association between mild OSA and sleepiness (35–39), and many others did not (28, 41–48, 50–53, 66, 68). In many cases, the focus of these studies was not sleepiness, and assessment of sleepiness was performed as part of a general description of the study population. None examined whether there were 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 more discordant. Of note, 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 (OR, 0.8; 95% CI, 0.3–2.0) (69). However, the risk for multiple MVAs over 5 years was not significantly increased in either sex. In another population study of 161 truckers, 34.8% of whom had mild OSA, there was no relationship between OSA severity and crash risk (OR, 0.82; 95% CI, 0.15–3.57 for a change in RDI of 1 SD) (65). In a case–control study, motor vehicle crash data from 3 years before polysomnography in individuals with suspected OSA were compared with 783 age- and sex-matched control subjects. Those with mild OSA had an increased relative risk (RR) of an MVA (RR, 2.6; 95% CI, 1.7–3.9) in comparison to controls (68). In a metaanalysis, Tregear and colleagues (70) found a nonsignificant trend for OSA severity as a risk factor for MVAs. Two other studies from clinic populations report conflicting results for those with mild OSA (71, 72).

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 (1,009 with mild OSA) and another in elderly women (178 with mild OSA) failed to show any association between mild OSA and the Functional Outcomes of Sleep Questionnaire (FOSQ) score (32, 33). However, in a large cohort study (SHHS) of middle-aged to elderly adults, including 1,672 with mild OSA, a reduction in the vitality component of the Short Form Medical Outcomes Survey (SF-36) was associated with mild OSA versus AHI less than 5/h (OR, 1.2; 95% CI, 1.02–1.43), although there was no association of the overall SF-36 score with mild OSA (54). Two other studies, one clinic based (41) and the other clinic and population based (67), used the Sleep Apnea Quality of Life Index (SAQLI) to assess quality of life and showed no adverse impact on quality of life from mild OSA.

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 were identified that examined the relationship between mild OSA and neurocognitive function. However, in the APPLES trial with both clinic- and community-based recruitment, there was no baseline correlation between AHI severity and any of the large number of neurocognitive tests performed (31). In a small clinic-based study, patients with no OSA and mild OSA had similar psychomotor vigilance test scores (55). Similarly, in a small community-dwelling population of veterans with post-traumatic stress disorder, there were no differences in neurocognitive test results according to OSA severity (73).

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) (74) assessed by the Zung Depression Scale. In this study, longitudinal change in AHI over 4-year intervals was also associated with change in depression status, but data for progression from no OSA to mild OSA or incidence data in those with mild OSA were not provided (74). Three other cross-sectional studies, two clinic based and one with mixed clinic and community recruitment, examined the association of mild OSA with mood (40, 41, 67) using a variety of different depression and anxiety scales: Beck Depression Inventory (41), State-Trait Anxiety Inventory (41), Profile of Mood States (67), Hamilton Rating Scale for Depression (67), and the anxiety and depression subscales of the Psychological General Well-Being Index (40). None found any association between assessments of either depression or anxiety with mild OSA.

In summary, there are discordant data examining the association between mild 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?

Summary of Evidence is provided in Table 2 and Table E4. Adherence to CPAP therapy was overall modest.

Daytime sleepiness. Twelve studies (75–86) reported on the effect of therapy on EDS. In a placebo-controlled, randomized crossover trial (78) assessing the effects of CPAP in a small group of subjects with mild OSA, no differences were observed in sleepiness between CPAP and a placebo pill at 1 month by either subjective (ESS on placebo [mean ± SE], 10.0 ± 1.2 vs. ESS on CPAP, 10.1 ± 1.4) or objective measures (Multiple Sleep Latency Test, mean sleep latency on placebo, 9.9 ± 1.5 min vs. CPAP, 10.0 ± 0.2 min). In a subsequent larger study by the same group (77) with a more symptomatic patient sample, significant improvement in subjective daytime sleepiness assessed by the ESS was reported after 4 weeks of CPAP compared with 4 weeks on oral placebo. (ESS at baseline, 13 ± 3; ESS on CPAP, 8 ± 4 compared with placebo pill, 11 ± 4; effect size, 0.75 for placebo vs. CPAP). However, no difference in objective sleepiness, as determined by Maintenance of Wakefulness Testing

Table 2. 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 (77). 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 (76). There were no changes in objective measures of sleepiness using MSLT/MWT (76, 77). 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 (78) or at 6 mo (80), respectively. In 1 study comparing radiofrequency surgery vs. sham, there was no change in the ESS at 4–6 mo (86), and in another, there was no improvement in the ESS scores after 1 yr of successful weight loss with diet and lifestyle modification (82).
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 (75), oral appliance (81), and upper airway surgery (85). In 1 study, there was no change in ESS after intervention with oral appliance (79).
Effect of therapy on quality of life		
5 randomized controlled trials and 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 (78). In another RCT, there was no significant difference in the SF-36 scores between radiofrequency surgery of soft palate and placebo applicator (86). However, in 3 RCTs, the SF-36 scores improved in a few domains with CPAP vs. placebo (76, 77) and with oral appliance vs. placebo (76), the FOSQ improved with CPAP vs. placebo (76), and the 15D questionnaire improved with very-low-calorie diet + lifestyle modification vs. lifestyle modification alone (82). In 1 nonrandomized study the SAQLI improved with CPAP (75).
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 (76, 80). 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 (77, 78).

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.

(CPAP, 16.2 ± 10.6 min vs. placebo, 14.4 ± 8.5 min), was observed between CPAP and placebo. In a 3-month randomized crossover study, the effects of CPAP, OA, and a placebo tablet on sleepiness were evaluated in subjects with mild to moderate OSA (76). In a planned *post hoc* analysis in those with mild OSA, both CPAP and OA were significantly better than placebo in improving the ESS (raw data not provided for mild OSA subgroup). In contrast, analysis of a subgroup of subjects with mild OSA in the APPLES RCT (80) found no differences in subjective sleepiness (ESS on CPAP, 8.4 ± 4.6 vs. sham CPAP, 7.6 ± 4.0) or objective sleepiness by Maintenance of Wakefulness Testing (sleep latency on CPAP, 17.8 ± 4.0 min vs. sham CPAP, 17.9 ± 3.3 min) between active CPAP and sham CPAP at 6 months. In contrast to other studies that included only sleep clinic populations, this study recruited from both the sleep clinic and the general population.

Two small RCTs did not demonstrate an improvement in the ESS scores after surgery (86) or weight loss (82) and on 2- to 5-year follow-up of the latter RCT (83, 84). Among observational studies, improvements in ESS have been reported with CPAP (75), OA (81), and surgery (85). The extent to which these responses are due to placebo effects is unclear because of the lack of control arms.

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 (75–78, 82, 86), including five RCTs

(76–78, 82, 86), 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 intervention with 4 weeks of CPAP compared with placebo (77). Five of the nine subscales of the SF-36 questionnaire showed significant improvements with CPAP (health transition, role-physical, bodily pain, social function, and vitality, with effect sizes 0.44–0.67). However, an earlier smaller clinical trial by the same group did not find significant effects on quality of life (78). Another RCT (76) also found that both CPAP and OA showed improvements on the FOSQ and total SF-36 scores compared with placebo ($P < 0.05$, no subscales reported). Three other small studies demonstrated discordant results, with improvement after CPAP (75) and weight loss (82) but not surgery (86).

In summary, most studies seem to show a small improvement on 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 (76–78, 80). In one of the first RCTs assessing the impact of CPAP on neurocognition, significant improvements were seen after 1 month in two out of seven cognitive tasks (Digit Symbol Substitution Task: effect size, 0.14; $P < 0.01$; 2-second Paced Auditory Serial Addition Test: effect size, 0.36) compared with an oral placebo (77). However, in an earlier study by the same group (78) a significant improvement was observed only in the Trail Making Task B, after 1 month of CPAP compared with placebo, but this was limited solely to the subgroup of subjects with good CPAP adherence (minimum 5 h use). All other neurocognitive tests showed no differences between CPAP and placebo. Of note, neither of these studies accounted for the multiple testing inherent in evaluating effects on several neurocognitive domains. In another study (76), improvements in neuropsychologic function on CPAP and OA were noted in a subset of subjects with mild OSA, but no specific information was provided. In contrast, no differences were observed in a large RCT (APPLES) at 6 months between subjects with mild OSA using CPAP and those using sham CPAP in three neurocognitive domains: Attention/Psychomotor Function (Pathfinder Number Test-Total Time), Learning and Memory (Buschke Selective Reminding Test-Sum Recall) and Executive/Frontal Lobe Function (Sustained Working Memory Test), as well as seven other secondary neurocognitive outcomes (80). Of note, 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 by the same group of authors (77, 78) used the Hospital Anxiety and Depression Scale (HADS) as a measure of minor psychiatric morbidity. Both studies showed significant improvement in the depression component of the HADS scale after 1 month of CPAP compared with placebo (effect size, 0.41) but not in the HADS anxiety score. 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, CAD, Cerebrovascular Events, Arrhythmias, and Cardiovascular and All-Cause Mortality?

Summary of Evidence is provided in Table 3 and Table E5. In performing the review for this question, it became apparent that there were five distinct clinical outcomes that needed to be addressed: hypertension, cardiovascular events, cerebrovascular accidents, cardiovascular and all-cause mortality, and arrhythmias. Evidence related to each of these will be summarized separately. As noted previously, the Task Force decided *a priori* to focus on outcomes of clinical relevance; hence, topics addressing surrogate markers of atherosclerosis, arterial stiffness, and heart remodeling and markers of metabolic dysfunction and inflammation were not evaluated.

Hypertension. There were five articles based on 4 longitudinal studies (17, 87–90) and 18 cross-sectional studies (8, 14, 16, 29, 38, 45, 46, 50, 51, 66, 91–98) that addressed the impact of mild OSA on hypertension.

Three of the longitudinal studies evaluated population-based cohorts (17, 87, 89). An analysis of the Wisconsin Sleep Cohort found that mild OSA was associated with an elevated risk of hypertension (17). This analysis included 132 subjects with mild OSA and evaluated hypertension risk at 4 years of follow-up adjusting for baseline hypertension status. Compared with those with an AHI of 0/h, those with mild OSA had an elevated unadjusted risk (OR) of hypertension of 2.74. After adjusting for age, sex, and obesity measures, the OR remained elevated at 2.03 (95% CI, 1.29–3.17). Compared with those with an AHI of 0.1/h to 4.9/h, the OR was 1.42 (95% CI, 1.13–1.78). In addition, over an average of 7.2 years of follow-up, the OR for developing an incident nondipping BP profile on 24-hour analysis was 3.1 (95% CI, 1.3–7.7) for systolic BP and 2.0 (95% CI, 0.7–5.6) for diastolic BP in those with mild OSA compared with those with AHI less than 5/h in analyses adjusting for important confounders such as age, sex, and body mass index (BMI) (90).

The SHHS followed individuals without hypertension, including 629 with mild OSA, for 5.2 years and assessed risk of incident hypertension (87). Unlike the Wisconsin Sleep Cohort, after adjusting for age, sex, and race, the OR for incident hypertension in those with mild OSA was 1.13 (95% CI, 0.90–1.43) and not statistically significant compared with those with an AHI less than 5 events/h. After additionally adjusting for BMI, the OR fell below 1.0 (OR, 0.89; 95% CI, 0.59–1.34 for overweight individuals; and OR, 0.92; 95% CI, 0.67–1.27 for obese individuals). Stratified analyses found no evidence for an elevated risk of hypertension in subgroups defined by age, sex, BMI, or degree of sleepiness.

Additionally, the Vittoria Sleep Cohort evaluated incident hypertension over an average of 7.5 years in a Spanish cohort that included 247 subjects with an RDI of 7 to 13.9 (89). Compared with those with an RDI less than 3, the unadjusted OR for incident hypertension was 1.84 (95% CI, 1.30–2.61) in those with mild OSA. However, after adjusting for multiple

Table 3. 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 mild OSA vs. control subjects (87–89), whereas in 1 cohort, the risk for incident hypertension was significantly increased in mild OSA vs. control subjects (17) with increased nondipping of BP with mild OSA (90). Eighteen cross-sectional studies: After adjusting for multiple confounders, there was an increased risk for hypertension or elevated BP in 1 population-based study (14). There was an increased percentage of individuals with high BP in mild vs. no OSA groups in another study (97). However, there was no increase in the risk for elevated BP or hypertension, after adjusting for confounders, in the remaining cross-sectional studies (8, 16, 29, 66, 91–94) where BP was the primary outcome, nor was there an increased risk in 9 additional studies (38, 45, 46, 50, 51, 95, 96, 98) 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 (99) or in CV events after a 20-yr follow-up (100). 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 (101) or was independently associated with coronary events during a 2.9-yr follow-up (102). 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 (46, 50, 51, 98, 104).
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 (20, 103, 113, 126). However, in 1 study mild OSA was independently associated with coronary events or death from cardiovascular causes (combined endpoint) (102).
Cerebrovascular accidents		
4 prospective observational cohort studies and 5 cross-sectional studies	Mean/median age in mild OSA groups ranged from 50 to 72 yr	In 3 prospective observational cohort studies (20, 100, 105), 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 for stroke with mild OSA vs. no OSA (106). In 5 cross-sectional studies (46, 50, 98, 104), 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 (107). In 2 smaller cross-sectional clinic-based studies, there was no association of cardiac arrhythmias with increasing severity of OSA (98) or no significant difference in the percent of patients with atrial fibrillation in the mild-OSA vs. no-OSA groups (46).
Cardiovascular and all-cause mortality		
CV 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 CV mortality in patients with mild OSA vs. no OSA (108, 109).
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 (100, 108, 109, 110, 127).

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

confounders, including age, sex, and BMI, the OR fell to 0.90 (95% CI, 0.61–1.34). Similar to the SHHS analysis, no evidence of differences by sex was found.

The Zaragoza Sleep Cohort reported on incident hypertension risk in a population recruited from a sleep clinic, and consequently it may be prone to selection bias (88). Over a median of 12.2 years of follow-up, 33.5% of the 355 individuals with mild OSA developed new-onset hypertension as compared with 25% of control subjects. After adjusting for important confounders it was unclear if those with mild OSA remained at elevated risk, as separate results for mild OSA are not reported. However, in adjusted analyses stratified by baseline level of sleepiness, those with mild OSA and not offered CPAP therapy were not at higher risk than control subjects. The hazard ratio (HR) was 1.24 (95% CI, 0.89–1.73) in those with ESS score less than 11 and 0.76 (95% CI, 0.39–1.56) in those with ESS greater than or equal to 11.

At least six population-based cross-sectional analyses of mild OSA and hypertension have been conducted (14, 16, 29, 91, 97). In five of the studies, the associations between these two conditions were not statistically significant (14, 16, 29, 91) after adjustment for important confounders such as age, sex, and obesity. However, in a population sample of women (97), there was a significantly higher prevalence of hypertension in mild OSA versus AHI less than 5/h. In contrast, in two large clinic-based cross-sectional analyses of mild OSA and hypertension (8, 92), there was no significant risk for hypertension in individuals with mild OSA versus control subjects after adjusting for relevant confounders.

Several studies completed in small primarily clinic populations, where hypertension was not the primary outcome, reported variable results. In brief, all but one of these studies (38, 45, 46, 50, 51, 95, 96, 98) did not find differences in the percentage of patients with hypertension or BP levels in patients with mild OSA compared with control subjects.

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 a number of prospective cohorts and a few cross-sectional studies. Gottlieb and colleagues performed a longitudinal study evaluating the risk of incident CAD and congestive heart failure (CHF) over 8.7 years by the presence and severity of OSA in the SHHS (99). Although OSA was a predictor of incident CAD and CHF in men with significantly elevated HRs in men with AHI greater than 30 compared with AHI less than 5/h, the HR for mild OSA compared with those with AHI less than 5/h was nonsignificant and less than 1.0 in all models including subgroups stratified by age and sex (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). Marshall and colleagues also found that mild OSA (n = 81 subjects) was not associated with cardiovascular events after a 20-year follow-up of 400 residents of the Western Australian town of Busselton (HR, 1; 95% CI, 0.6–1.7) (100).

In contrast, the Wisconsin Cohort Study (101) found that after 24 years of follow-up, the incidence of cardiovascular events in the mild OSA group was 16.2 per 1,000 years, with a significantly increased risk of combined coronary heart disease and CHF in those with mild OSA compared with the no OSA group (adjusted HR, 1.9; 95% CI, 1.05–3.5) after excluding patients on CPAP. When participants treated with CPAP were included in the analysis, the HR for coronary heart disease and CHF remained significant (adjusted HR, 2.51; 95% CI, 1.43–4.41). Of note, the risk was higher in women (HR, 4.6; 95% CI, 1.5–14.6) than men (HR, 1.1; 95% CI, 0.5–2.1). Similarly, although there is the potential risk of referral bias, in a clinical cohort study among consecutive patients aged 50 years or older referred for a sleep study (102), mild OSA was found to be independently associated with coronary events or death from cardiovascular causes (combined endpoint) during a 2.9-year follow-up (HR, 2.22; 95% CI, 1.10–4.45).

Retrospective analysis of a large clinical cohort of patients referred for sleep studies showed no association of mild OSA with different composite outcomes. Kendzerska and colleagues evaluated a composite outcome (myocardial infarction, stroke, CHF, revascularization procedures, or death from any cause) during a median follow-up of 68 months (103). The authors found that 1,172 (11.5%) of 10,149 participants experienced the composite outcome. No association of mild OSA with the composite cardiovascular endpoint was identified compared with those without OSA (103). Several cross-sectional analyses also did not find an association between mild OSA and cardiovascular events (46, 50, 51, 104).

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. Evidence exploring the association of mild OSA and cerebrovascular accidents was derived from both prospective observational cohorts and cross-sectional analyses. Three longitudinal studies failed to demonstrate an association between mild OSA and stroke (20, 100, 105). A longitudinal study of incident stroke from the community-based SHHS showed a progressively higher crude incidence rate of stroke with increasing obstructive AHI. However, after covariate adjustment, there was no increase in stroke risk in the second quartile (AHI, 4.05/h–9.5/h) in comparison to the first quartile (AHI $<$ 4.0/h) of the AHI distribution for both men (HR, 1.86; 95% CI, 0.67–5.12) and women (HR, 1.34; 95% CI, 0.76–2.36) (105). Additionally, the population-based Busselton cohort study reported that mild OSA was not independently associated with incident stroke after a 20-year follow-up of 397 residents (HR, 1.0; 95% CI, 0.39–2.7) (100).

In a clinic-based study, the incidence of a composite outcome of stroke or death was determined according to the presence and severity of OSA (20). In a trend analysis, greater severity of OSA at baseline was associated with an increased risk of the development of the composite endpoint. However, the HR for individuals with mild OSA (defined as AHI 4/h–12/h) was not significantly elevated (HR, 1.75; 95% CI, 0.88–3.49) for the combined endpoint compared with those with AHI less than

4/h. Moreover, the majority of events were deaths rather than stroke. In contrast to the aforementioned evidence, in one prospective observational cohort study, the impact of OSA on the incidence of stroke, death, or myocardial infarction after 10 years of follow-up was ascertained in patients with CAD referred for coronary angiography. In this dataset, mild OSA was independently associated with risk of stroke (HR, 2.44; 95% CI, 1.08–5.52) (106).

Cross-sectional analyses of a large population-based cohort (104) as well as small clinic-based studies (46, 50, 98) did not find differences in the percentage of patients with stroke in mild-OSA versus no-OSA groups.

In summary, mild OSA is 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 CAD.

Arrhythmias. One population-based study (MrOS Sleep Study) studied the association between mild OSA and nocturnal arrhythmias in elderly men. Although increasing quartile of RDI was associated with increased odds of atrial fibrillation and complex ventricular ectopy, the study did not find an increased risk for atrial fibrillation or complex ventricular ectopy in patients with mild OSA versus no OSA (107). In one cross-sectional clinic-based study (98), there was a trend for occurrence of paroxysmal atrial and ventricular complexes, sinus bradycardia, and sinus pause on the polysomnography study with increasing severity of OSA compared with no OSA; however, the risk for arrhythmia in mild OSA alone was not analyzed. In a retrospective study of a clinic-based veteran population (46), there was no significant difference in the percent of patients with atrial fibrillation in the mild-OSA versus no-OSA groups (6.6 vs. 3.5%).

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

Cardiovascular and all-cause mortality. Several cohorts have consistently found that mild OSA is not associated with increased cardiovascular mortality. In the 18-year follow-up of the Wisconsin Cohort Study, it was found that mild OSA was not associated with cardiovascular mortality (HR, 1.8; 95% CI, 0.7–4.9) (108). In a Korean sleep clinic population, there was no increase in cardiovascular mortality (HR, 0.32; 95% CI, 0.03–3.57) in patients with mild OSA, and only severe OSA was associated with increased cardiovascular mortality as compared with subjects without OSA (109).

There was no increase in all-cause mortality in the mild OSA group in the population-based Busselton cohort after 20 years of follow-up (HR, 0.51; 95% CI, 0.27–0.99) (100). All-cause mortality was also not significantly increased in the mild OSA group compared with the no-OSA groups in the Wisconsin cohort after 8 years of follow-up (adjusted HR, 1.6; 95% CI, 0.8–2.8) (108), in the SHHS after 8.2 years of follow-up (adjusted HR, 0.93; 95% CI, 0.80–1.08) (110), or in a Korean sleep clinic population (HR, 0.91; 95% CI, 0.36–2.28) (109).

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?

Summary of evidence is provided in Table 4 and Table E6. The scope of this PICO question was to examine whether therapies for OSA alleviate adverse cardiovascular consequences, which includes hypertension, CAD, arrhythmias, heart failure, cerebrovascular disease, cardiovascular disease–related mortality, and all-cause mortality. Six studies were identified with relevant data. Five of the six studies examined treatment effects on BP, and one study examined treatment effects on cardiovascular events and survival. With the exception of one study, all studies recruited from either sleep or otolaryngology clinics. There were no studies of the impact of treatment of mild OSA on stroke, cardiovascular events, atrial fibrillation, or other arrhythmias.

Hypertension. There was one RCT with relevant data (82). Participants were followed over 5 years in two additional publications available for extraction (83, 84). The initial report randomized patients with mild OSA to either an intensive lifestyle intervention or a control arm and followed patients over 1 year (82). Participants in the intervention group lost more weight than the control group (10.7 kg vs. 2.4 kg, respectively) and had a greater resolution of OSA (63 vs. 35%, respectively). In contrast to observational studies, no significant changes in systolic or diastolic 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 (83), 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-yr findings), despite evidence of some weight regain in the intervention group. Interestingly, a significant reduction in systolic BP was reported in the control group; however, 7 of 18 (39%) participants 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 (84), a significantly greater percentage of patients in the intervention group than in the control group no longer had OSA (10 of 20 [50%] vs. 4 of 37 [11%], respectively). No significant changes in systolic or diastolic BP were reported between these two groups at this time point.

The Zaragoza Sleep Cohort (88) examined the effects of CPAP in specifically the patients with mild OSA (n = 355). They found no significant differences in the risk of developing hypertension among patients who were ineligible for CPAP (n = 255; crude incidence rate per 100 person-years [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).

In a longitudinal study, patients with hypertension and OSA underwent nonstandardized surgical treatment for their OSA (111). In those with mild OSA, although the postoperative AHI was still increased (8/h ± 6/h), improvements in mean 24-hour systolic (preoperative: 160 ± 5 mm Hg vs. postoperative: 144 ± 1 mm Hg), daytime systolic (165 ± 11 mm

Table 4. 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 (82) vs. conventional care at 1 yr. Subsequent follow-up at 2 and 5 yr (83, 84) did not find significant changes in systolic or diastolic BP between the 2 groups. However, the antihypertensive medications were discontinued in 39% of participants in the intervention group vs. 14% in the control group (83). In 1 retrospective cohort (112) with normal BP at baseline and 1 nonrandomized intervention study (111), there was a significant decrease in the mean arterial BP with CPAP vs. no CPAP therapy (112) and a decline in the mean 24-h systolic or diastolic BP with evidence of dipping (111) after upper airway surgery vs. before surgery or in comparison to the no OSA group, respectively. In a prospective observational cohort (88), 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 was 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 (113). 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.

Hg vs. 148 ± 10 mm Hg) and diastolic (98 ± 15 mm Hg vs. 94 ± 10 mm Hg), and nocturnal systolic BP (148 ± 13 mm Hg vs. 139 ± 14 mm Hg) 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 (112), 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 participants with untreated OSA. Similar findings were found when the treated mild OSA group was matched to a subgroup of the untreated mild OSA group on the basis of a propensity score.

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, 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 that reported the effects of CPAP in patients with mild OSA on all-cause mortality (113). 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 nonrandomized 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 were no studies assessing the impact of treatment on cardiovascular mortality.

Limitations

It should be reiterated that there are several caveats to the interpretation of the evidence regarding mild OSA. The most important of these is the decision to define mild OSA severity according to the parameters proposed in the 1999 Chicago criteria even though these were formulated at a time when thermistors were commonly used to assess airflow and definitions of hypopnea were more conservative. Thus, studies in which airflow was recorded using thermistor alone would possibly have had a higher AHI if assessed by the currently recommended nasal pressure technique. Similarly, studies in which hypopneas were identified using the occurrence of an arousal in addition to a desaturation criterion would likely have had a higher AHI than if only desaturation was used. In studies where events were scored using nasal pressure signals in comparison to thermistor signals, the AHI was clearly significantly higher using nasal pressure in both general (18/h vs. 11/h, $P < 0.05$) and clinic populations (37/h vs. 27/h, $P < 0.001$) (114–116), and the impact

may be greater for subjects with mild OSA (117, 118). Thus, studies in which airflow was recorded using a thermistor alone, subjects recruited using a definition of AHI between 5/h and 15/h would possibly have a higher AHI (i.e., moderate OSA) if assessed by the currently recommended nasal pressure technique.

In 2000, Redline and colleagues highlighted the impact of using differing definitions of "hypopnea" in the SHHS cohort and demonstrated a 10-fold change in calculated prevalence of OSA and up to a 27 events/h change in median AHI on the basis of the definition chosen (119). The 2007 American Academy of Sleep Medicine scoring manual recommended that a hypopnea be defined as a 30% reduction in airflow, as measured by the nasal pressure transducer flow signal, with a concomitant 4% drop in oxygen saturation; alternatively, a hypopnea could be defined as a 50% or greater decline in the flow signal associated with a 3% drop in oxygen saturation and/or an EEG arousal lasting for at least 3 seconds (61). However, if the same sleep studies are scored using these two different hypopnea definitions, there is considerable variability in the median AHI (8.3/h vs. 14.9/h with the recommended and alternative definitions, respectively) (64). The 2012 American Academy of Sleep Medicine update to the scoring manual defined hypopnea as a 30% or greater reduction in flow lasting at least 10 seconds and associated with either oxygen desaturation of greater than or equal to 3% or an arousal, thus incorporating arousals into the standard definition of hypopnea (59). Consequently, it is important to be cautious when comparing results of studies performed in different laboratories using dissimilar definitions of AHI. For instance, in the study by Quan and colleagues (67), where AHI with 3% desaturation and arousals (AHI3A) was used for OSA diagnosis, no difference was seen in ESS between AHI3A less than 5/h and AHI3A 5/h to 15/h. However, without an arousal criterion, both the AHI3A less than 5/h and the AHI3A 5/h to 15/h might be similar to a cohort with AHI with 4% desaturation in the range 0/h to 5/h (i.e., including many "normal" subjects). Barnes and colleagues, in contrast, did find an improvement in the ESS score on CPAP but defined "mild" OSA as 5/h to 15/h using a thermistor, which may correspond to a significantly higher AHI measured with a nasal cannula (i.e., including "moderate" subjects) (76). Until a large study is performed with a sensitive index and multiple cut-points or thresholds spanning 5 to 30 events/h, it will be difficult to conclusively separate "normal," "mild," and "moderate" OSA. However, it is biologically improbable that the impact of OSA is determined by thresholds or cut-points of OSA severity, whether they are defined by the AHI or another metric. Thus, although the task force considered all studies with AHI data between 5/h and 15/h as mild OSA as equivalent, it is likely that the boundaries between normal and mild OSA, and between mild and moderate OSA, are indistinct. As noted earlier, a significant limitation is that "mild" classification of disease is dependent on an index and does not relate to potential underlying heritable and nonheritable factors that may define the syndrome of OSA.

Another limitation in the literature was the paucity of studies in which there were direct comparisons of mild OSA to no OSA. In many studies, the AHI was treated as a continuous variable and a trend analysis was performed. Thus, the impact of mild OSA could not be independently assessed. Furthermore, a number of analyses combined mild OSA with moderate OSA or used a definition of mild OSA other than the Chicago criteria. Thus, some relatively prominent studies were excluded from consideration (120–124). Studies did not examine whether elderly age, sex, or race/ethnicity modified the impact of mild OSA or its treatment on neurocognitive outcomes. In addition, not all studies adjusted for relevant confounders, including physical inactivity, obesity, salt intake, race, family history, caffeine, hyperlipidemia, use of antihypertensive or cardiac medications, and smoking, and thus may not be comparable. It is uncertain whether studies using devices that did not directly measure sleep were equivalent to those that used full polysomnography. Most studies did not separately analyze outcomes in individuals with and without sleepiness. Not all intervention studies provided pre–post data for each intervention arm. CPAP adherence was suboptimal in many studies, often 4 hours or less per night. Suboptimal adherence likely contributed to a decrease in treatment efficacy. In addition, studies used different therapeutic approaches (e.g., weight loss, OA, upper airway surgery, CPAP) to treating OSA, with variable improvement in the AHI precluding direct comparison of the impact of treatment on mild OSA. Moreover, some studies had an insufficient number of events to answer the research question posed.

Finally, the methodological rigor in BP measurements was variable. Measurement of BP did not always follow recommended guidelines by the American Heart Association, American Society of Hypertension, or other expert organizations. Specifically, there was no uniformity in measuring BP with respect to the time of day, the number of measurements, or whether a 24-hour ambulatory BP, office BP, or sleep laboratory BP were used.

Knowledge Gaps

On the basis of detailed and comprehensive appraisal of the literature, multiple knowledge gaps and opportunities were identified. For the sake of clarity, the knowledge gaps were grouped into separate categories as described below:

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 MVAs related to mild OSA is understudied. In addition, whether treatment of mild OSA has any beneficial impact on the risk for MVAs 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 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, or mood, and treatment thereof.

Cardiovascular Outcomes

1. It is unclear whether mild OSA plays a causal role in elevating BP or increasing the risk of incident hypertension.
2. There is a lack of large-scale RCTs 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 versus no OSA.
2. There are limited studies on the impact of non-PAP therapies, including OAs, surgery, and 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 predominance and neurocognitive and/or cardiac outcomes or whether treatment of this condition improves these outcomes.

Research Recommendations

The following are 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, OA, 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 MVAs and whether patients on adequate therapy for mild OSA have lower event rates than 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, OA, 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 versus 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.

Conclusions

Mild OSA is a highly prevalent disease with potential adverse neurocognitive and cardiovascular complications. There is evidence that patients with mild OSA who demonstrate subjective sleepiness may benefit from treatment of the disorder. In addition, in general populations, mild OSA does not appear to be associated with elevated mortality risk. However, there is inconclusive evidence regarding the impact of mild OSA on neurocognition, quality of life, mood, elevated 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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