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CLINICAL REVIEW

Untreated obstructive sleep apnea and the risk for serious long-term adverse outcomes: A systematic review

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SUMMARY

Background: Reports on the association between obstructive sleep apnea (OSA) and risk of death, cardiovascular (CV) events, diabetes and depression have been inconsistent.
Methods: We conducted a systematic review of the prognostic value of clinical and polysomnographic (PSG) characteristics of OSA for adverse long-term outcomes of untreated OSA in adult patients. A comprehensive search strategy for prognosis studies, OSA, CV events, mortality, depression and diabetes was developed in collaboration with a medical information specialist. All English language studies, from Jan 1999 to Dec 2011, with longitudinal design in adults with OSA diagnosed by PSG recording, found through Medline, Embase and bibliographies of identified articles, were considered eligible. Quality was assessed using published guidelines.
Results: Among 26 articles, ten evaluated the association of OSA with mortality, 9 with a composite CV outcome, 4 with stroke, 2 with diabetes and 1 with depression. Significant relationships between the apnea–hypopnea index (AHI) and outcomes of interest were reported in 18 studies: seven for all-cause mortality, six for composite CV events, three for stroke, one for diabetes and one for depression. The effect of AHI was attenuated by female gender, older age, absence of daytime sleepiness and higher body mass index. Due to clinical heterogeneity between studies, meta-analyses were not performed.
Conclusion: Evidence exists in men for a relationship between OSA and all-cause mortality and a composite CV outcome. Associations between OSA and other outcomes remain uncertain. Among OSA-specific markers, only AHI was a consistent predictor. Other consistent predictors were traditional CV risk factors. Research is required to identify effect modifiers and the predictive ability of various AHI threshold values and hypopnea definitions. An enhanced set of OSA-specific predictors will allow better risk stratification to guide OSA treatment.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repeated episodes of upper airway obstruction during sleep.[1] It affects an estimated 9% of women and 24% of men.[2,3]

There are plausible biological pathways (through chronic intermittent hypoxemia, sleep fragmentation, hemodynamic disturbances and alterations in sympathetic activity) through which untreated OSA might lead to death, cardiovascular (CV) events, diabetes or depression (Fig. 1).[4–9] However, reports on the causal relationship between OSA and such sequelae have been inconsistent.[10–23] There is also little known about which specific clinical and physiological factors best predict the occurrence of these adverse outcomes in OSA.[23] In addition, it is unknown if the thresholds for diagnosing and treating OSA should be the same in people with CV disease and those who are otherwise healthy,[23] or if the presence of OSA changes the effect of traditional risk factors for CV events and mortality. We conducted a systematic review of untreated OSA in adult patients with two goals: a) to examine the relationship between OSA and death, CV events, diabetes and depression; and b) to determine the prognostic value of demographic, clinical and polysomnographic (PSG) characteristics of

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Abbreviations

AHI	apnea–hypopnea index
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CHF	congestive heart failure
CV	cardiovascular
CVD	cardiovascular disease
DS	daytime sleepiness
HR	hazard ratio
HTN	hypertension
IHD	ischemic heart disease
MI	myocardial infarction
OHS	obesity-hypoventilation syndrome
OR	odds ratio
OSA	obstructive sleep apnea
PSG	polysomnographic
RDI	respiratory disturbance index
RR	relative risk
SaO_2	oxygen saturation
SHHS	Sleep Heart Health Study
TST	total sleep time
WSCS	Wisconsin Sleep Cohort Study

OSA on these long-term outcomes. Non-disease outcomes such as motor vehicle or occupational accidents, although important, were not examined in the current review.

Methods

Data sources and searches

In collaboration with disease experts and a medical information specialist, we developed a comprehensive search strategy for prognostic studies of OSA with outcomes of myocardial infarction (MI), stroke, mortality, depression and diabetes.[24] All English language peer-reviewed studies published from Jan 1999 to Dec 2011 with prospective or retrospective data collection and a longitudinal design,[25] found through Medline, Embase and bibliographies of identified articles and reviews, were considered eligible. Basic search terms used are presented in Table S1.

Inclusion criteria

We included studies that targeted adult patients with a diagnosis of OSA on the basis of the apnea–hypopnea index (AHI) made by PSG recording and followed them for at least one year. We excluded studies without an untreated OSA group or where more than 50% of participants were pregnant or had previous CV events or other severe neurological or psychiatric diseases. For more details see Appendix A.

The serious adverse outcomes (either objectively documented or self-reported) considered were: CV events, both non-fatal and fatal; all-cause mortality; diabetes; and depression. All available clinical and PSG variables were treated as potential predictors; however we report on only those with a statistically significantly association with our outcomes in at least one study. Predictors were collated into four domains: patient demographic characteristics, medical history, physical exam findings, and OSA characteristics (clinical symptoms, PSG indexes, treatment options).

Study selection

Two independent reviewers (TK, TM) assessed study titles and abstracts. If the title or abstract suggested that the study might meet the inclusion criteria, both reviewers assessed the full article. Differences of opinion were resolved by discussion. A third reviewer (GT) was consulted where consensus could not be reached.

Data extraction and quality assessment

Study quality was assessed independently by two reviewers (TK, TM) using guidelines developed by Hayden et al., for assessing prognostic studies.[26] The appraisal had two steps. The first step assessed the items related to six potential sources of bias (study participation and attrition; prognostic factor and outcome measurements; confounding measurement and account; and analyses). The second step judged presence of potential biases as "Yes", "Partly", "No", or "Unsure". For studies with sufficiently high quality, we abstracted data on the relationships between our outcomes and both clinical information and PSG indices.

To summarize the level of evidence, we used a system similar to the Scottish Intercollegiate Guidelines Network (SIGN) methodology[27]: i) "++" when all or most of the quality criteria proposed by Hayden et al. were fulfilled (allowing one "Partly" while appraising all potential sources of bias); ii) "+" when some of the criteria were fulfilled; iii) "–" when few or no criteria fulfilled (at least one "Yes"). Additionally, as proposed by SIGN, studies with

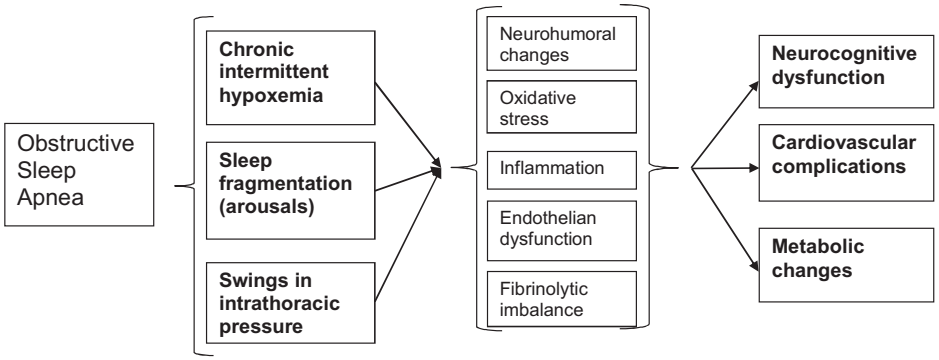

Fig. 1. The long-term consequences of untreated obstructive sleep apnea (OSA): possible links (modified from Tasali and Ip (2008)), Bradley and Floras (2009), Knoepke and Aloia (2009), Bagai (2010) and Sharma and Kavuru (2010).

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