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Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: A meta-analysis of prospective cohort studies

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ABSTRACT

Background: The association between obstructive sleep apnea (OSA) and the incidence of cardiovascular disease (CVD) has been examined in many studies. However, the findings are not entirely consistent across studies. Our goal was to evaluate the association between OSA and risk of CVD and all-cause mortality by performing a meta-analysis of prospective cohort studies.
Methods: We used generalized least squares regression models to estimate the dose–response relationship. Heterogeneity, subgroup, and sensitivity analyses and publication bias were performed.
Results: Twelve prospective cohort studies involving 25,760 participants were included in the meta-analysis. The overall combined relative risks for individuals with severe OSA compared with individuals with an AHI of <5 were 1.79 (95% confidence interval [CI]: 1.47 to 2.18) for CVD, 1.21 (95% CI: 0.75 to 1.96) for incident fatal and non-fatal coronary heart disease, 2.15 (95% CI: 1.42 to 3.24) for incident fatal and non-fatal stroke, and 1.92 (95% CI: 1.38 to 2.69) for deaths from all-causes. A positive association with CVD was observed for moderate OSA but not for mild OSA. The results of the dose–response relationship indicated that per 10-unit increase in the apnea–hypopnea index was associated with a 17% greater risk of CVD in the general population.
Conclusions: This meta-analysis of prospective cohort studies suggests that severe OSA significantly increases CVD risk, stroke, and all-cause mortality. A positive association with CVD was observed for moderate OSA but not for mild OSA.

1. Introduction

Obstructive sleep apnea (OSA) is characterized by frequent episodes of total and/or partial collapse of upper airways during sleep, resulting in recurrent episodes of intermittent hypoxemia and arousal from sleep [1,2]. This disorder affects approximately 24% of men and 9% of women [1,3]. There is emerging research evidence for an independent association between OSA and cardiovascular disease (CVD) [4–11]. However, the magnitude of the association has varied across studies and a causal link has not yet been convincingly documented. A recent meta-analysis [12] synthesized available data from nine studies, one of which [13] was based on a retrospectively selected population. In addition, the review did not consider whether data from clinic-based cohorts might affect the size or significance of the true association. Potential publication bias was also not fully explored in this report. Given that OSA is a treatable disease, a better understanding of the relationship between OSA and the risk of CVD will have important public health and clinical implications given the possibility that prevention and treatment of OSA could decrease the incidence of cardiovascular events. In addition, it has been stated that long-term continuous positive airway pressure (CPAP) improves cardiovascular risk in patients with OSA [14,15]. However, to our knowledge, there is no study available that evaluates the impact of long-term CPAP treatment on cardiovascular risk in patients with OSA through meta-analysis.

Therefore we conducted a meta-analysis of prospective cohort studies to assess the magnitude of the association of OSA and risk of CVD and to estimate whether increased severity of OSA is associated with increased CVD risk. Also, we evaluate the impact of CPAP therapy on improvement of cardiovascular risk.

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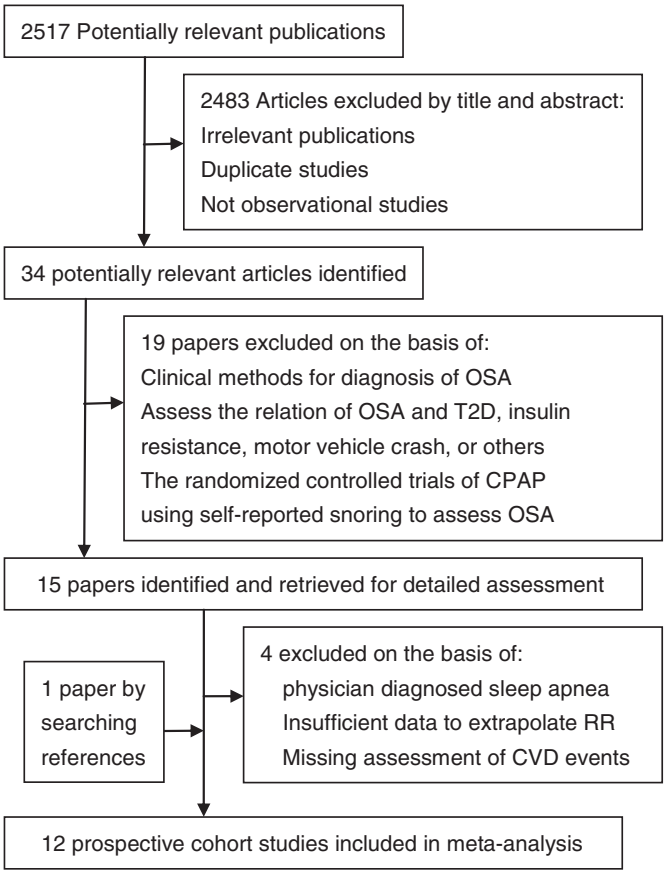

Fig. 1. Flow chart of study selection. Flow chart shows literature search for prospective cohort studies of obstructive sleep apnea in relation to cardiovascular events and all-cause mortality. CPAP = continuous positive airway pressure; CVD = cardiovascular disease; OSA = obstructive sleep apnea; RR = relative risk; T2D = type 2 diabetes.

2. Methods

2.1. Search strategy

We attempted to follow the Meta-Analysis of Observational Studies in Epidemiology guidelines throughout the design, implementation, analysis, and reporting for this present meta-analysis [16]. We performed a systematic search through September 2012 for published articles using PubMed, Embase, ISI Web of Knowledge, and the Cochrane Library databases. The following search terms were used: 1) obstructive sleep apnea, sleep-disordered breathing, and CPAP therapy; 2) cardiovascular diseases, cardiovascular death, myocardial infarction, angina, ischemic heart disease, coronary disease, heart failure, cerebrovascular disorders, stroke, death, mortality, and all-cause mortality; and 3) prospective studies, follow-up studies, and cohort studies. No restrictions were imposed on the type or language of publications. In addition, we found more articles through a manual search of the reference lists from retrieved original papers and recent reviews.

2.2. Study selection

We first conducted an initial screening of all abstracts and then selected articles for full-text examination. We only included prospective cohort studies in which the presence of OSA was assessed by the use of objective measurement. Studies were excluded if self-reported surrogate parameters such as snoring were used to assess OSA. To be included in the meta-analysis, studies also had to meet the following criteria: 1) the exposure of interest was OSA; 2) the outcome of interest was CVD, coronary heart disease (CHD), stroke, or all-cause mortality; and 3) the assessment of relative risk (RR) and the corresponding 95% confidence interval (CI) for OSA categories were reported.

2.3. Validity assessment

The quality of all included studies was assessed using a modified scoring system, which allowed a total score of 0–6 points (6 refers to the highest quality) on the basis of MOOSE [16], QUATSO [17], and STROBE [18]. The system allocated one point each when (a) appropriate inclusion and exclusion criteria; (b) diagnosis of CVD, stroke, CHD, and all-cause mortality was based on accepted clinical criteria; (c) OSA was assessed with a validated method; (d) adjustments were made for age, sex, body mass index, and smoking status; (e) any other factors were adjusted (such as diabetes, hypertension, or hyperlipidemia); and (f) other any justification was given for the cohort.

2.4. Data extraction

Two authors independently extracted the data using a standardized data extraction form. To resolve discrepancies about inclusion of studies and interpretation of data, a third investigator was consulted, and consensus was reached by discussion. The following characteristics of the identified studies were recorded: first author's last name, publication date, country, follow-up (years), number and characteristics of participants and age at baseline, assessment method of OSA, the severity of OSA in different categories, outcomes reported, ascertainments of outcomes, and adjustments for potential confounding factors.

The presence or absence of OSA at baseline was the key exposure variable. OSA was defined as the average number of apneic plus hypopneic episodes per hour of sleep, assessed using the apnea–hypopnea index (AHI). According to the American Academy of Sleep Medicine classification of OSA severity, an AHI of <5 was defined as normal, 5–15 as mild, 15–30 as moderate, and >30 as severe [19]. We collected exposure data including the definitions and categories for OSA, the number of participants with OSA, and the duration of follow-up.

In most studies, individuals with an AHI of <5 served as the reference group. In two studies, patients with an AHI of <10 [20] and people with no apnea to mild to moderate OSA (AHI 0–29) [21] constituted the comparison group. Although we included the three studies in our analysis, we conducted a restricting analysis that only included studies with a reference group strictly defined as individuals with an AHI of <5.

Outcomes of interest in the present study included major CVD (fatal and nonfatal), stroke (fatal and nonfatal), CHD (fatal and nonfatal), and all-cause mortality. CVD refers to nonfatal or fatal CVD events, but not CVD risk factors. We recorded exposure data including the definitions and criteria of cardiovascular outcomes, the numbers of participants with OSA who did and did not have the outcomes, and the multivariable adjusted risk estimate.

2.5. Statistical analyses

We used RR as a common measure of the association between OSA and risk of CVD, CHD, stroke, or all-cause mortality across studies. When a study reported the risk estimates for different levels of adjustment for covariates, we used the risk estimate from the most fully adjusted models in the analysis of the pooled RR.

Based on the severity of OSA, we estimated the corresponding pooled RR for the primary end point of incident cardiovascular events and death. For those studies that stratified participants by categories of OSA, we used the corresponding RRs to different OSA categories. Three studies [9,21,22] only reported OSA group versus the reference group and didn't report in detail the risk estimates according to OSA categories. In these cases, to avoid overestimation of the effect of OSA, we treated the risk estimates of OSA as severe OSA categories. For two studies [10,14] that reported risk estimates separately for more specific cardiovascular outcomes, we used a fixed-effects model to calculate a combined risk estimate for the main analysis.

Between-study homogeneity of RRs across studies was assessed by using the Cochran's Q test (significance level at $P < 0.10$) [23]. The I^2 statistic was also calculated to quantify the proportion of inconsistency across studies [24]. We computed the combined risk estimates using the DerSimonian and Laird [25] random effects model to obtain the pooled RR. For the current study, random-effects models were more appropriate due to the presence of heterogeneity among these studies compared with fixed-effects models.

According to sex, geographic region, duration of follow-up, recruitment strategy, and sample size, subgroup analyses were performed to evaluate the impact of these factors on the association between severe OSA and CVD risk. Sensitivity analyses were further conducted to examine possible explanations for heterogeneity and to explore the effect of various exclusion criteria and individual cohorts on the overall risk estimate. Because of rather small numbers of studies for other outcomes, the sensitivity and subgroup analyses were only performed for severe OSA and CVD risk.

To further estimate the dose–response relationship between AHI and risk of CVD, we conducted regression analysis using generalized least squares regression models [26]. This model allows the estimation of a weighted average of the log RRs across all studies, with the weight partially dependent on the inverse of the variance of the log of the RR. Potential publication bias was detected with visual inspection of contour-enhanced funnel plots [27], Egger linear regression test [28], and the Begg rank correlation test at the $P < 0.10$ level of significance [29]. If publication bias was indicated, we further assessed the number of missing studies in a meta-analysis by application of the trim and fill method and recalculated the pooled RR estimate with the addition of those missing studies [30]. We performed all analyses using STATA version 11.2 (StataCorp LP, College Station, Texas). Except where otherwise specified, a P value <0.05 was considered statistically significant.

3. Results

3.1. Literature search

The initial search yielded 2517 potentially relevant citations from the electronic reference databases, of which 34 articles met the inclusion