Association of Obstructive Sleep Apnea With Risk of Serious Cardiovascular Events
A Systematic Review and Meta-Analysis

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Background—The relationship between obstructive sleep apnea (OSA) and cardiovascular events remains unclear. We conducted a systematic review to determine the incident risk of cardiovascular events among patients with OSA.

Methods and Results—We searched MEDLINE and EMBASE in January 2011 for prospective studies that followed up patients with OSA for incident ischemic heart disease, stroke, and cardiovascular mortality. Outcomes data were pooled using random effects meta-analysis and heterogeneity assessed with the I^2 statistic. Regression analysis was performed to evaluate the effects of different gradations of OSA severity based on apnea-hypopnea index. We identified 9 relevant studies from 1731 citations. OSA was associated with incident stroke in a meta-analysis of 5 studies (8435 participants), odds ratio (OR) 2.24; 95% confidence interval (CI), 1.57–3.19; I^2=7%. A significant association was seen in studies that were predominantly on men; OR, 2.87; 95% CI, 1.91–4.31, whereas data on women were sparse. In the overall analysis of 6 studies (8785 participants), OSA was nonsignificantly associated with ischemic heart disease (OR, 1.56; 95% CI, 0.83–2.91), with significant findings in the 5 studies that recruited mainly men (OR, 1.92; 95% CI, 1.06–3.48). Substantial heterogeneity was noted (I^2=74%). OSA was linked to cardiovascular death in 2 studies involving 2446 participants (OR, 2.09; 95% CI, 1.20–3.65, I^2=0%). Regression analysis showed greater likelihood of stroke or cardiovascular events with increasing apnea-hypopnea index values.

Conclusions—OSA appears to be associated with stroke, but the relationship with ischemic heart disease and cardiovascular mortality needs further research.   (*Circ Cardiovasc Qual Outcomes*. 2012;5:720-728.)

Cardiovascular disease is the leading cause of death in the United States. Soaring rates of obesity correlate with an increasing incidence of obstructive sleep apnea (OSA), a recently hypothesized risk factor for ischemic heart disease (IHD) and ischemic stroke. Whether OSA independently increases their incidences, or whether this relationship is confounded by this population's prevalent cardiovascular risk factors, remains debated.

Although multiple studies have sought to identify whether OSA independently increases cardiovascular risk, their variable methodologies and results have hindered definitive conclusions. Furthermore, no meta-analysis of prospective studies has hitherto been performed. In light of OSA's increasing prevalence and treatability plus the recent US Million Hearts campaign to prevent 1 million heart attacks and strokes in the next 5 years,[1] we aimed to perform a systematic review and meta-analysis to identify whether OSA independently increases the risk of incident IHD, ischemic stroke, and cardiovascular mortality.

Methods
Search Strategy and Study Selection
In January 2011, we searched MEDLINE and EMBASE (Ovid SP) using the terms listed in online-only Data Supplement Appendix I, limited to English-language and human studies. We also checked the reference lists of included studies and relevant review articles. Two reviewers (C.S.K. and A.N.) independently checked titles and abstracts against the eligibility criteria and obtained full-text versions of potentially relevant studies, which were then discussed with Y.K.L. and P.K.M. before final decision on inclusion.

Eligibility Criteria
We selected prospective studies that recruited patients who had been diagnosed with OSA through standardized polysomnography, and who had no reported history of recent acute myocardial infarction or

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WHAT IS KNOWN

- Although some studies have suggested a potential association between obstructive sleep apnea and adverse cardiovascular outcomes, the variations in study design and quality have caused difficulty in judging the magnitude and significance of the postulated link.

WHAT THE STUDY ADDS

- We identified 9 relevant studies in our systematic review and conducted a meta-analysis of the association between obstructive sleep apnea and patient-relevant outcomes such as stroke, ischemic heart disease, and cardiovascular mortality.
- Obstructive sleep apnea was significantly associated with incident stroke: odds ratio, 2.24, (95% confidence interval, 1.57–3.19), and cardiovascular mortality odds ratio 2.09 (95% confidence interval, 1.20–3.65), with regression analysis indicating greater risk with higher levels of the apnea-hypopnea index.
- The link between obstructive sleep apnea and ischemic heart disease remains less certain due to substantial heterogeneity among the studies, although evidence from studies recruiting male participants predominantly does suggest a likely association odds ratio 1.92 (95% confidence interval, 1.06–3.48).

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stroke. Relevant studies had to have a longitudinal follow-up duration of >1 year, and to report on the risk of cardiovascular outcomes compared with controls (without OSA or with varying degrees of OSA severity). The primary outcomes of interest for inclusion in the meta-analysis were IHD and cerebrovascular events (including stroke and transient ischemic attacks [TIAs]). Eligible studies had to report (or provide sufficient data to enable the calculation of) the odds ratio (OR) or relative risk of cardiovascular disease in patients with OSA compared with controls.

Use of continuous positive airway pressure ventilation or baseline evidence of stable cardiovascular disease were not cause for exclusion (provided that the studies fulfilled all the other eligibility criteria), but we planned to subject any such studies to further sensitivity analysis.

Data Extraction

We extracted information on study design, date, and location of study, enrollment criteria and demographic details of participants, follow-up period, and outcomes. Data were recorded onto a preformatted Excel spreadsheet by C.S.K. and checked by W.B. Outcome data were independently extracted by C.S.K. and Y.K.L., and checked by W.B. All discrepancies were resolved after discussion and cross-checking against the primary papers.

Validity Assessment

We recorded the methods used in diagnosing OSA and the subsequent ascertainment of serious cardiovascular events (including losses to follow-up). Where available, we noted the extent of adjustment for confounding factors between groups. We planned to assess publication bias using the funnel plot, provided that the meta-analysis had >10 studies, with no evidence of significant heterogeneity. To minimize outcome reporting bias, we also contacted authors for missing outcome data.
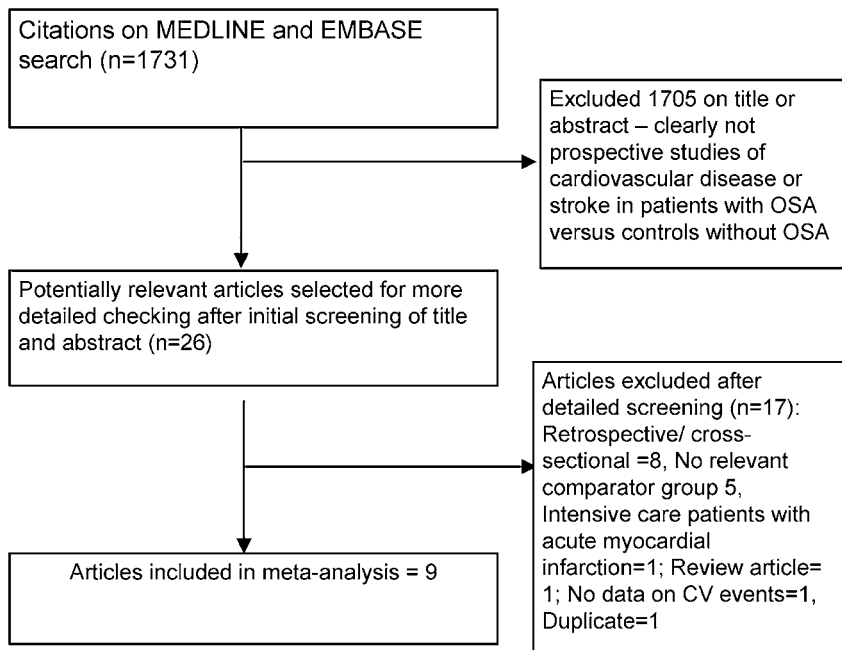
Data Synthesis

The risk statistics from each individual study were pooled in a meta-analysis by Y.K.L. using RevMan 5.1 software (Nordic Cochrane Center, Kobenhavn, Denmark).[2] We used a random effects model, which takes study heterogeneity into account to generate the pooled ORs for OSA as an associated risk factor for (1) IHD, (2) stroke, or (3) cardiovascular death/overall mortality. Heterogeneity was assessed using the I^2 statistic.[3]

For meta-analysis of IHD, the outcomes included were angina, myocardial infarction, or revascularization procedure. For incident stroke, we included outcomes that were reported as stroke, ischemic stroke, or TIA. We evaluated mortality (cardiovascular or overall) as a secondary outcome.

Additional prespecified sensitivity analysis was performed based on exclusion of studies that provided unadjusted data only. Post hoc sensitivity analysis was conducted based on exclusion of studies that used different parameters in participant selection or outcome definitions.

Figure 1. Flow diagram of the process of article selection for meta-analysis.

Secondly, we carried out regression analysis to model the relationship between the quantitative measure of apnea-hypopnoea index (AHI) and likelihood for stroke or cardiovascular death. We used variance weighted least-squares regression (vwls command in Stata version 10.0, StataCorp, College Station, TX) for paired AHI values and their respective ORs, as compared with a reference category of AHI <5. Where ranges of AHI were given in individual studies, we used the midpoint of the range in the analysis. For studies that did not describe the upper bounds of the range (eg, simply listed AHI as >30), we used either the mean from that particular study, or the midpoint AHI averaged from 2 studies that reported an AHI >30.[4,5] Although we believe this is a reasonable approximation, we also performed sensitivity analysis that excluded AHI values if the upper ranges were not known.

Results

The search yielded 1731 studies, of which 9 were finally included in the review (Figure 1).[4–12] Some studies reported separately on stroke and coronary outcomes from datasets with partial overlap of participants, namely the Sleep Health Study Cohort in the articles from Gottlieb et al and Redline et al[5,7] whereas participants from Yale were reported in the Shah et al and Yaggi et al articles.[11,12] These studies were handled separately in the meta-analysis and forest plots to avoid double-counting. In total, 2446 patients were meta-analyzed for risk of cardiovascular death, 8785 for risk of IHD, and 8435 for ischemic stroke.

Characteristics of the studies that were used in meta-analysis are summarized in Table 1. In short, 3 studies investigated the risk of IHD,[7,10,11] 4 assessed the risk of stroke (with 2 studies including TIAs),[5,6,9,12] and 2 studies evaluated both coronary and cerebrovascular disorders.[4,8] One study separately compared OSA with snorers and to those without sleep-disordered breathing,[4] whereas 3 compared OSA with snorers alone,[10–12] 3 compared OSA with those without sleep-disordered breathing,[6,8,9] and 2 reported separately on men and

Table 1.   Study Design and Patient Characteristics

Study	Study Design, Location, Year(s)	Participants	% White	Mean Age	% Men	Mean BMI Study Group	% With AF by Study Group	Patient Selection	Key Exclusion Criteria
Arzt et al[6]	Community cohort; Wisconsin; 1988.	1189	Not disclosed	47	55	30	0% (prevalent stroke group)	Stratified random sample state employees aged 30–60 y enrolled in sleep cohort study.	History of stroke before entry in study, unstable cardiopulmonary disease, airway cancer, incomplete sleep study data.
Gottlieb et al[7]	Community cohort; multiple locations across the United States (baseline data 1995–1998)	4422	78%	Median 62	43.5	30.1	Not disclosed	Adults >40 y who were enrolled in large-scale epidemiological cardiopulmonary studies.	CHD, heart failure, incomplete sleep study, and missing data for BMI, blood pressure, smoking and lipid measurements.
Marin et al[4]	Cohort from outpatient sleep clinic; Zaragoza, Spain; 1992–1994	1010	Not disclosed	50	100	28.5	Not disclosed	Men with OSA referred to sleep unit; included those who declined CPAP. Healthy controls from community sleep apnea study.	Patients excluded from control arm if history of snoring or excessive daytime somnolence, or AHI >5.
Mooe et al[8]	Cohort; Umea, Sweden; teaching hospital; 1992–1995.	408	Not disclosed	60	68	Not disclosed	Not disclosed	Age <70 with stable angina undergoing coronary angiography.	Incomplete sleep study.
Munoz et al[9]	Community cohort; Vitoria, Spain; 1999.	394	Not disclosed	Median 77	57.1	28.8	20% (stroke) vs 4.6% (no stroke)	Subsample of community participants (age 70–100 y) enrolled in sleep apnea prevalence study.	Unstable cardiopulmonary or end-stage disease, airway tumours, previous sleep-disordered breathing, previous stroke.
Peker et al[10]	Cohort from outpatient sleep clinic; Gothenburg, Sweden; 1991.	308	Not disclosed	49	79.5	28.6	Not disclosed	Age 30–69 y, with history of snoring/apnea investigated at sleep laboratory.	CAD or heart failure at baseline.
Redline et al[5]	Pooled data from 7 community cohorts; multiple locations across the United States (baseline data 1995–1998)	5422	80%	Median 63	45.4	28.0	4.7% (stroke) vs 0.96% (no stroke)	Adults >40 y who were enrolled in large-scale epidemiological cardiopulmonary studies.	Current treatment with CPAP/oral appliance, previous stroke, missing/ inadequate data.
Shah et al[11]	Cohort from outpatient sleep clinic; Yale University, New Haven, CT; 1997–2001.	1436	86%	60	69.4	34	5% (OSA) vs 4% (control)	Age >50 y referred for evaluation of sleep-disordered breathing.	History of MI or stroke, missing baseline data, previous tracheostomy.
Yaggi et al[12]	Cohort from outpatient sleep clinic study; Yale University, New Haven, CT; 1997–2000.	1022	87%	60	71.3	33.8	7% (OSA) vs 4% (control)	Age >50 y referred for evaluation of sleep-disordered breathing.	History of MI or stroke, missing baseline data, previous tracheostomy.

REM indicates rapid eye movement; CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; BMI, body mass index; and atrial fibrillation, AF.

women with OSA.[5,7] Median follow-up duration varied from 2.9 to 12 years.

Patients aged >30 years were recruited from community and hospital settings across Europe and the United States. Included cohorts comprised patients with[4,8,9] and without[5–7,10–12] baseline cardiovascular disease and compared them against snorers and those without sleep-disordered breathing. Treatment of OSA with continuous positive airway pressure varied from 0% to 50%, but compliance with treatment was inadequately assessed or reported to subanalyze.

Validity Assessment

Patients were recruited from the general population,[5–7,9] sleep clinics,[4,10–12] and an angiography clinic.[8] Diagnosis of OSA was through overnight polysomnography in all the studies,

with standardized assessment of AHI except for 1 study where the investigators did not have the equipment to measure hypopnea, and OSA was defined by the frequency of overnight oxygen desaturations (>30 events/h).[10] A variable proportion of patients were lost to follow-up (up to 18%); some studies excluded such patients from analysis. Although this may have led to uncertainty around effect sizes for nonfatal events, all studies searched death registers for fatal events (Table 2).

We note that confounding remains a source of bias; some studies did not identify and adjust for all potential risk factors, including alcohol consumption,[7,8,10,13] hypercholesterolae-mia,[8,10] and use of lipid-lowering drugs,[6,8,10] antihypertensives[6,8] and antiplatelets.[4,5,8–10] Some studies addressing ischemic stroke did not specifically assess previous TIAs[4–6,9,12] and atrial fibrillation (AF).[4,8]

Table 2.   Study Outcomes, Results and Risk of Bias

Study	Risk Factor Adjustment	Outcomes and Ascertainment	Follow-Up	Results
Arzt et al[6]	Age, sex, and BMI.	Stroke (n=14). Based on patient reports of stroke diagnosis made by physicians, with date of event and treatment.	4 y; only 371 patients had data by final visit.	Fully adjusted: AHI >20 vs <5 OR, 3.08 (0.74–12.81)
Gottlieb et al[7]	Age, race, BMI, smoking, cholesterol, lipid-lowering medications, diabetes mellitus, blood pressure, and antihypertensives.	Composite of incident MI (n=185), coronary death (n= 76), or revascularization (n=212) from ICD-9 codes or medical records. Blinded adjudicating committee.	8.7 y; 476 participants initially excluded due to missing data.	Fully adjusted (men) AHI >30 vs <5 HR, 1.33 (0.91–1.95),women: AHI >30 vs <5 HR, 0.40 (0.12–1.27)
Marin et al[4]	Age, CV disease, diabetes mellitus, hypertension, lipid disorders, smoking or alcohol use, blood pressure, glucose and lipid levels, CV drugs.	Fatal cardiovascular events (MI, stroke, n=55); from medical records, death certificates, direct contact with physicians, or patient's family, Social Security Death Index.	10.1 y; 26 lost to follow-up.	OSA vs healthy men: untreated mild–moderate OR, 1.15 (0.34–2.69); untreated severe OR, 2.87 (1.17–7.51).
Mooe et al[8]	Age, sex, BMI, hypertension, diabetes mellitus, left ventricular function, and coronary intervention.	Stroke /TIA (n=33), MI (n=29), and death (n=28) from autopsy findings, medical records, and contacting patients or their relatives. Blinded outcome assessors.	5.1 y (median); 15 excluded due to incomplete data.	AHI >10 vs AHI <10, adjusted HR: stroke OR, 2.98 (1.43–6.20). Unadjusted RR: MI, 1.02 (0.49–2.14); Death RR, 1.46 (0.71–3.00)
Munoz et al[9]	Sex	Ischemic stroke (n=20) ascertained by ICD-9 codes and review of medical records by blinded neurologist.	4.5 y (mean); 11 subjects excluded.	Adjusted HR for AHI >30 vs <30 was 2.52 (1.04–6.10).
Peker et al[10]	Age, sex, BMI, smoking, diabetes mellitus, hypertension, lung disease, blood pressure, use of antihypertensives.	CAD events (n=28, incident angina or MI) from ICD codes in Swedish Hospital Discharge Register.	7 y; 14 excluded due to missing data.	RR for incident CAD 4.60 (1.83–11.6) in patients with OSA at baseline.
Redline et al[5]	Age, BMI, smoking, blood pressure, antihypertensives, diabetes mellitus, and race.	Ischemic stroke (n=193) from direct contact with patients, hospital discharge data, death certificates. Adjudicated by trained abstractors who reviewed medical records and test results.	8.7 y (median) IQR 7.8–9.4 y; 21 lost to follow-up, 102 CPAP users excluded.	Adjusted HR:(men) AHI >19 vs AHI <4 was 2.86 (1.10–7.39),(women) AHI >19 vs AHI <4 was 1.21 (0.65–2.24),
Shah et al[11]	Age, race, gender, sex, smoking status, alcohol consumption, BMI, atrial fibrillation, hypertension, hyperlipidaemia, diabetes mellitus.	MI, heart failure, coronary artery revascularization procedures; postal questionnaire or telephone contact with patients or relatives. Blinded adjudication of medical records. Total = 53 major coronary events and 33 cardiovascular deaths.	2.8 y 390 participants (27%) lost to follow-up.	Coronary artery events and cardiovascular death: AHI >30 vs <5 adjusted HR 2.82 (1.46–5.45), unadjusted CV death AHI >5 vs <5, HR, 1.70 (0.92–3.16)
Yaggi et al[12]	Age, race, gender, sex, smoking status, alcohol, BMI, atrial fibrillation, hypertension, and lipids.	Stroke (including TIA); ascertained by self- postal questionnaire or telephone contact with patients or relatives. Blinded adjudication of medical records. Total = 24 strokes and 64 deaths.	3.4 y 180 (18%) participants lost to follow-up.	Stroke: AHI >5 vs AHI <5, unadjusted RR, 3.02 (1.27–7.21), Death adjusted RR, 1.70 (0.92–3.16)

AHI indicates apnea-hypoapnea index; BMI, body mass index; OR, odds ratio; HR, hazard ratio; MI, myocardial infarction; CAD, coronary artery disease; CV, cardiovascular; TIA, transient ischemic attack; RR, relative risk; IQR, interquartile range; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; and ICD, *International Classification of Diseases*.
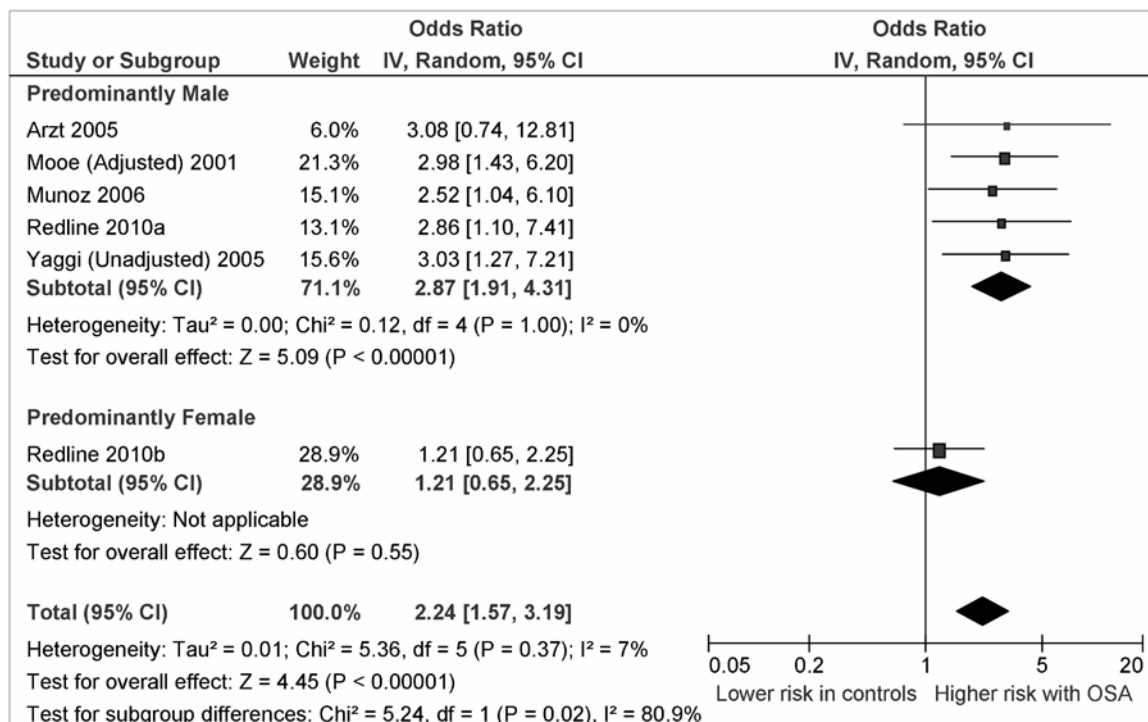
Figure 2. Meta-analysis of obstructive sleep apnea (OSA) and associated risk of stroke.

Pooled Analysis

Stroke (5 Studies, n=8435)

Overall, OSA was significantly associated with incident stroke (OR, 2.24, 95% confidence interval [CI], 1.57–3.19), Figure 2.[5,6,8,9,12] Subanalysis by sex found a significant OR, 2.87 (95% CI, 1.91–4.31) in men, but a nonsignificant OR, 1.21 (95% CI, 0.65–2.25), based on the single study that provided specific data on women.[5] There was no evidence of substantial heterogeneity in the analysis of stroke.

AF is a well-recognized risk factor for ischemic stroke, and it has been suggested that OSA may increase the tendency to develop AF.[14] Hence, we recorded any differences in the rates of AF between study groups and any reported impact of AF in patients with OSA and stroke (Table 1). Of the 5 studies included in our meta-analysis of ischaemic stroke, only 1 failed to report on the presence of AF.[8] Three studies found different rates of AF in OSA or stroke patients compared with controls[5,9,12] (Table 1). In Munoz's cohort the presence or absence of AF did not influence the risk of stroke.[9] Equally, other studies found that adjusted analysis with AF as a covariate,[12] or exclusion of patients with AF,[5] did not change the reported relationship between OSA and stroke. Finally, although Arzt et al[6] did not report on AF and incident stroke, they stated that AF was not present in any of the patients with prevalent stroke.

IHD (6 studies, n=8785)

OSA was also found to be a significant risk factor for IHD in predominantly male studies (OR, 1.92; 95% CI, 1.06–3.48), though the single study that reported specifically on women participants[7] suggested no clear association with OSA (OR, 0.4; 95% CI, 0.12–1.30); consequently, the overall OR for both sexes combined is nonsignificant (OR, 1.56; 95% CI,

0.83–2.91).[6–8,10–12] This meta-analysis was also limited by substantial heterogeneity (I^2=74%) (Figure 3).

Cardiovascular death (2 studies)[4,11] or overall mortality (2 studies)[8,12] (Figure 4) OSA was found to significantly increase the risk of cardiovascular death in pooled analysis (OR, 2.09; 95% CI, 1.20–3.65), with a trend toward increased overall mortality (OR, 1.59; 95% CI, 1.00–2.55), with no evidence of statistical heterogeneity.

Sensitivity Analysis

To assess the effect of variations in quality, as well as possible sources of heterogeneity, a number of sensitivity analyses were conducted. We looked at the exclusion of those studies with baseline cardiovascular disease, as well as those where TIAs were included in stroke outcomes. We also evaluated the effect of excluding the 3 studies that provided unadjusted data (and are thus prone to confounding),[8,11,12] as well as excluding the only study that was unable to measure the AHI.[10] The mean age of participants (77 years) in 1 study was higher than in the other studies,[9] but exclusion of this particular study did not affect our findings. Overall, the sensitivity analyses did not lead to any change in the statistical significance or direction of effect for any of the outcomes assessed, although the sources of heterogeneity still remain unclear (Table 3).

Regression Analysis

In the regression analysis, AHI was associated with a significant increase in likelihood of stroke or cardiovascular death (P<0.001; Figure 5).[4–6,11,12] A 10-unit incremental increase in AHI was associated with a greater OR of 1.36 (95% CI, 1.26–1.43) for adverse outcomes of stroke/cardiovascular death. Sensitivity analysis excluding AHI with missing values for the upper bound of the range showed a very similar OR of
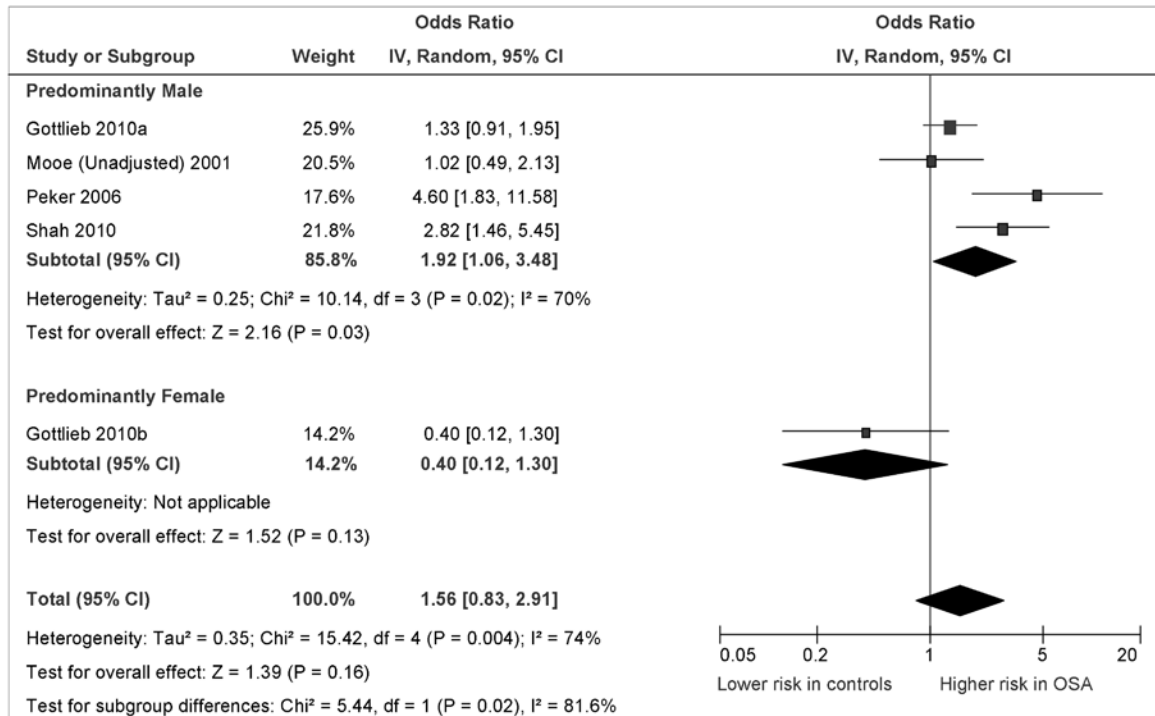
Figure 3. Meta-analysis of obstructive sleep apnea (OSA) and associated risk of ischemic heart disease.

1.35 (1.25–1.47) for stroke or cardiovascular death with every 10-unit incremental increase in AHI.

There were 2 overlapping studies from a single center that reported on different cardiovascular outcomes. If we excluded the earlier Yaggi study that focused on stroke,[12] the analysis showed an OR of 1.35 (95% CI, 1.25–1.45) for every 10-unit increase in AHI. The later study by Shah et al[11] had a greater number of participants and reported on coronary artery disease and cardiovascular death; exclusion of this study from the analysis resulted in an OR of 1.22 (95% CI, 1.13–1.32) for every 10-unit increase in AHI.

Owing to how the data was originally presented, it was not possible to separate the causes of death further or to separate stroke from cardiovascular death within the regression analysis; these data should mainly reflect the impact of severity of OSA on risk of stroke, because most of the studies here reported on cerebrovascular end points. (online-only Data Supplement Appendix II)

Discussion

Our meta-analysis supports existing evidence that OSA is an independent risk factor for stroke incidence (OR, 2.24, 95%
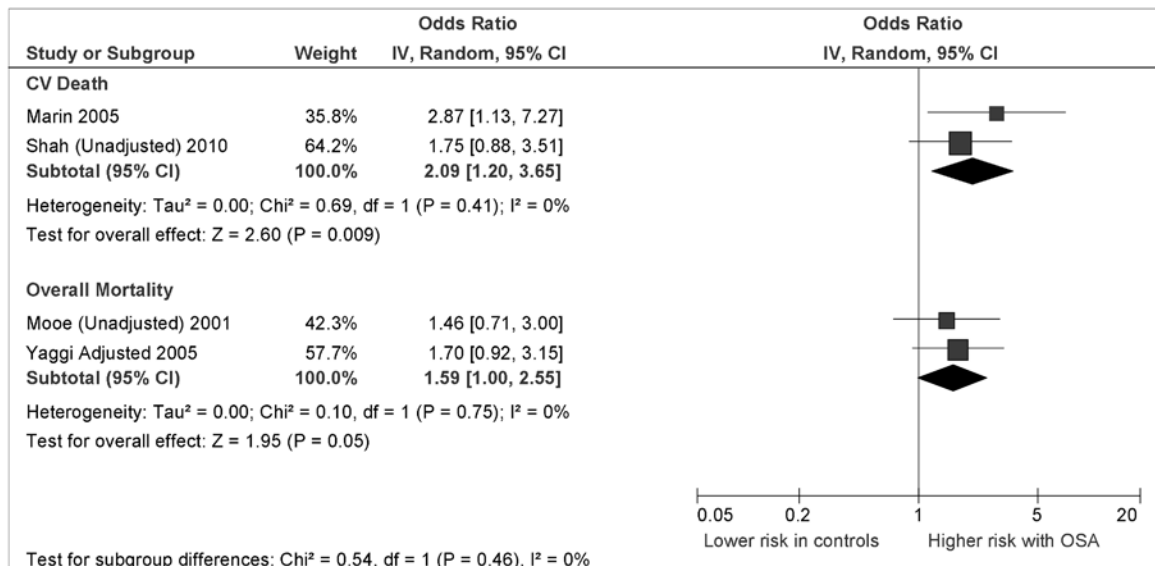

Figure 4. Meta-analysis of obstructive sleep apnea (OSA) and associated risk of cardiovascular or overall mortality.

Table 3.   Sensitivity Analysis

	Outcome	Sensitivity Analysis (95% CI)	Heterogeneity, %
Exclude Mooe and Yaggi (outcomes included TIA)[8,12]	Stroke	1.93 (1.19–3.12)	16
Exclude Mooe unadjusted[8]	CAD	1.72 (0.79–3.75)	79
Exclude Mooe and Shah unadjusted[8,11]	CV death or overall mortality	2.00 (1.19–3.34)	0
Exclude Yaggi unadjusted[12]	Stroke	2.15 (1.42–3.24)	16
Exclude Peker (AHI not assessed)[10]	CAD	1.26 (0.69–2.30)	68
Exclude Munoz (elderly population)[9]	Stroke	2.25 (1.46–3.48)	24

CAD indicates coronary artery disease; CV, cardiovascular; TIA, transient ischemic attacks; and AHI, apnea-hypopnoea index.

CI, 1.57–3.19; $P<0.001$), and cardiovascular mortality (OR, 2.09; 95% CI, 1.20–3.65; $P=0.009$). Moreover, we established a plausible dose–response relationship by demonstrating that each 10-unit incremental increase in apnea-hypopnea index (AHI) was significantly associated with a relative increase of 36% in the odds of having a cerebrovascular event. Our estimates remained robust to a variety of sensitivity analyses. We also verified previous conclusions that OSA is more strongly associated with stroke than IHD, and that men appear most susceptible,[13] although data on women are still lacking. As OSA affects 4–14% of the Western population,[15] the population impact and cardiovascular burden is likely to be substantial.

We did not find a consistent link between OSA and IHD, although there appeared to be a potential link in male participants. This may reflect the different pathophysiology involved in stroke compared with heart disease, and in women as compared with men. The inability to demonstrate a significant association in women may either be due to the relatively limited sample size or the greater impact of other cardiovascular risk factors in women. For instance, a recent systematic review found that cigarette smoking in women conferred a proportionately higher risk of coronary heart disease as compared with the risks from cigarette use in men.[16]

Our results should be set in the context of the existing literature. A previous meta-analysis reported that patients with stroke and TIA often had sleep-disordered breathing.[17] However, this other meta-analysis cannot demonstrate a plausible temporal link because it did not look at incident stroke during follow-up among patients with OSA. Our results also support the finding that there is increased risk of stroke among patients with coronary artery disease and sleep apnea.[18] In terms of mortality, the findings of this review are compatible with the findings of an Australian study that reported sleep apnea to be an independent risk factor for cardiac causes of mortality.[19]

The Pathogenesis of OSA-Related Cardiovascular Events

There is still some uncertainty regarding the exact mechanisms behind the increased risk of cardiovascular disease in patients with OSA. The American Heart Association (AHA) and American College of Cardiology (ACC) have recently published a comprehensive review indicating that there were potentially at least 6 different mechanisms at play.[14] Episodes of obstructive apnea can cause intermittent hypoxemia, CO_2 retention, oxygen desaturation, as well as altered autonomic and hemodynamic responses. This can lead to surges in blood pressure due to sympathetic activation and release of vasoconstrictive substances such as endothelin.[14] There remains some debate regarding other mechanisms, such as oxidative stress, endothelial dysfunction, and insulin resistance, that may increase risk of cardiovascular disease with OSA. However, interpretation of current data are limited by the cross-sectional design of certain studies,[20] and the presence of a wide range of confounding factors such as existing comorbidities and other cardiovascular risk mediators.[14]
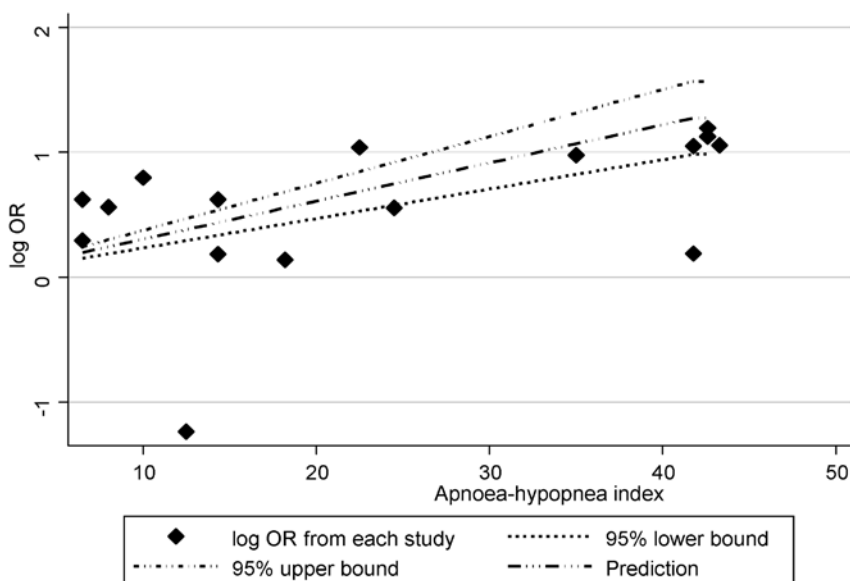
Figure 5. Regression analysis for odds ratio of stroke or serious cardiovascular events according to degree of apnea-hypopnoea index (AHI).

To reduce the possibility of confounding, Butt et al[21] recently looked at normostensive patients with moderate–severe OSA (with no apparent cardiovascular disease), and performed myocardial perfusion imaging as compared with 2 sets of matched controls without OSA (hypertensive patients and healthy subjects). Patients with OSA were found to have significant abnormalities in myocardial perfusion, as well as attenuated brachial artery reactivity when compared with healthy controls, thus lending support to the hypothesis regarding endothelial dysfunction in OSA. Nevertheless, this remains a hotly debated area where the actual mechanisms are likely to involve several pathways, and more rigorous research is required to untangle the relative contribution of each pathological process.

AF is a known risk factor for ischemic stroke, but the AHA/ACC review has previously considered the relationship between OSA and AF to be unproven,[14] and more recent reviews have yet to resolve this issue. Ng et al[22] performed a meta-analysis that demonstrated a significant association between OSA and recurrent AF after catheter ablation. In contrast, Loomba et al[23] reported inconsistent findings on the link between OSA and incident or prevalent AF, with statistically significant results arising mainly from retrospective studies. Gami et al[24] reported that OSA was not independently associated with incident AF in patients above the age of 65 years. Equally, the studies included in our review did not show any conclusive link between AF and stroke in patients with OSA.

Limitations

Although we have generally relied on adjusted data, we acknowledge that confounding and differences in patient selection is a possible source of bias. However, the development of hypertension and insulin resistance in OSA and their role in atherosclerosis pathogenesis may actually oppose adjusting for these factors due to the risk of underestimating the effect of OSA on cardiovascular morbidity.[25]

There was substantial heterogeneity in the analysis of incident IHD, and we were unable to identify the source of heterogeneity. Outcome measures and categories of AHI were inconsistently reported and we have attempted to address this by carrying out a regression analysis according to reported AHI, rather than just a dichotomized model based on presence or absence of OSA. Selective outcome reporting and publication bias remain a possibility as we did not receive a good response rate from contacting authors for additional published or unpublished data. Our search was limited to English-language studies only.

Implications for Further Research

There are subgroups of patients who warrant future study. Our data are derived mainly from studies with a predominance (55–79%) of men. There is much less evidence to accurately quantify the risk in women. Given that our data show a significant link, a prospective assessment of cardiovascular morbidity in lean patients with OSA may help to confirm OSA's etiological role in atherosclerotic pathogenesis. Conduct of a randomized controlled trial will provide stronger evidence of cause and effect. However, existing trials of continuous positive airway pressure have generally been of short duration, and focused on the assessment of surrogate markers rather than hard end points.[26] Hence, the feasibility of a longer term trial with clinical outcomes needs to be carefully considered.

Conclusions

Current evidence suggests that OSA may be an independent risk factor for stroke and cardiovascular mortality. In contrast, the strength of any potential association between OSA and IHD remains unclear due to imprecision and inconsistencies in the data. More high-quality studies are needed to evaluate these relationships and how the risk associated with OSA compares with other modifiable cardiovascular risk factors (ie, hypertension, diabetes mellitus, smoking) as identified by the INTERHEART study.[27] Additional studies are needed to determine whether better management of OSA leads to fewer cardiovascular events.

Disclosures

None.

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Association of Obstructive Sleep Apnea With Risk of Serious Cardiovascular Events: A Systematic Review and Meta-Analysis

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Supplemental Material

Appendix 1. Methods

Search strategy: EMBASE and MEDLINE in Ovid SP January 2011 using .mp suffix

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

(myocardial-infarction.mp OR cerebrovascular.mp OR cardiovascular.mp OR stroke.mp)

AND

sleep-apnea.mp.

AND

obstructive.mp.

Limited to human and English language.

Appendix 2. Results: Data used in regression analysis

Study	Outcome	OSA Severity	OR	LL	UL
Arzt 2005 [1]	Incident stroke	Referent: AHI <5	1	1	1
Arzt 2005 [1]	Incident stroke	AHI 5-20	0.29	0.04	2.36
Arzt 2005 [1]	Incident stroke	AHI >20	3.08	0.74	12.81
Redline 2010 [2] (men)	Incident ischaemic stroke	Referent:AHI 0-4.05	1	1	1
Redline 2010 [2] (men)	Incident ischaemic stroke	AHI 4.05-9.5	1.86	0.67	5.12
Redline 2010 [2] (men)	Incident ischaemic stroke	AHI 9.5-19.13	1.86	0.7	4.95
Redline 2010 [2] (men)	Incident ischaemic stroke	AHI 19.13-164.5	2.86	1.1	7.39
Redline 2010 [2] (women)	Incident ischaemic stroke	Referent: AHI 0-4.05	1	1	1
Redline 2010 [2] (women)	Incident ischaemic stroke	AHI 4.05-9.5	1.34	0.76	2.36
Redline 2010 [2] (women)	Incident ischaemic stroke	AHI 9.5-19.13	1.2	0.67	2.16
Redline 2010 [2] (women)	Incident ischaemic stroke	AHI 19.13-164.5	1.21	0.65	2.24
Shah 2010 [3]	CAD events or CV death	Referent: AHI <5	1	1	1
Shah 2010 [3]	CAD events or CV death	AHI 5-14	2.22	1.1	4.45
Shah 2010 [3]	CAD events or CV death	AHI 15-29	2.65	1.27	5.56
Shah 2010 [3]	CAD events or CV death	AHI >30 (mean = 35)	2.82	1.46	5.45
Marin 2005 [4]	Cardiovascular death	Untreated mild OSA (mean 18.2)	1.15	0.34	2.69
Marin 2005 [4]	Cardiovascular death	Untreated severe OSA (mean 43.3)	2.87	1.17	7.51

Yaggi 2005 [5]	Stroke or Death	AHI 4-12	1.75	0.88	3.49
Yaggi 2005 [5]	Stroke or Death	AHI 13-36	1.74	0.87	3.51
Yaggi 2005 [5]	Stroke or Death	AHI >36	3.3	1.74	6.26

OR = odds ratio, LL = lower bounds of 95% CI, UL = upper bounds of 95% CI, CAD

= coronary artery disease, CV = cardiovascular.

Supplemental References
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