

# Obstructive Sleep Apnea and Serious Adverse Outcomes in Patients with Cardiovascular or Cerebrovascular Disease

## *A PRISMA-Compliant Systematic Review and Meta-Analysis*

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**Abstract:** Obstructive sleep apnea (OSA) is seen in approximately 60% to 70% of patients with stroke or ischemic heart disease (IHD). The relationship between OSA and recurrent vascular events and all-cause mortality remains inconclusive. We aimed to systematically evaluate the associations between OSA and serious adverse outcomes following stroke or IHD by a meta-analysis of prospective cohort studies.

We searched MEDLINE and EMBASE in August 2014 for studies that evaluated the prospective associations between OSA and the risk of stroke, IHD, and death among stroke or IHD patients. Outcome data were pooled using random effects meta-analysis. Subgroup, heterogeneity, and sensitivity analyses and publication bias were performed.

Of 13 hospital-based cohort studies included, 5 reported results on stroke (n = 860), 6 reported on IHD (n = 1083), and 11 reported on all-cause death or cardiovascular death (n = 1930). OSA was significantly associated with the risk of stroke, IHD, and all-cause mortality after stroke or IHD. The pooled relative risks were 1.94 (95% confidence interval [CI], 1.29–2.92) for stroke, 1.83 (95% CI, 1.15–2.93) for IHD, and 1.59 (95% CI, 1.33–1.89) for all-cause mortality. There was no evidence of significant between-study heterogeneity. The results did not materially change in the sensitivity analyses for the outcomes of stroke and all-cause mortality.

OSA may be a significant predictor of serious adverse outcomes following stroke or IHD. More high-quality studies are needed to determine if better treatment of OSA leads to fewer recurrent vascular events, especially a large-scale, multicenter randomized-controlled trial.

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**Abbreviations:** AHI = apnea-hypopnea index, CI = confidence interval, CPAP = continuous positive airway pressure, HR = hazard ratio, IHD = ischemic heart disease, OSA = obstructive sleep apnea, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized-controlled trial, RR = relative risk.

## INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway and affects approximately 18% of middle-aged adults.<sup>1,2</sup> A recent meta-analysis that combined the results from 9 prospective cohort studies reported that OSA was significantly associated with stroke in participants without previous cardiovascular disease.<sup>3</sup> Furthermore, previous observational studies suggested that long-term continuous positive airway pressure (CPAP) treatment improved cardiovascular risk in patients with OSA.<sup>4,5</sup> Compared with the general population, patients with stroke or ischemic heart disease (IHD) have a 3- to 4-fold higher prevalence of OSA, approximately 60% to 70%.<sup>6,7</sup> It is possible that treating OSA could improve clinical recovery in those patients.<sup>8</sup> Therefore, OSA has been considered as a potential new treatment target for patients with stroke or IHD.<sup>1,8,9</sup> However, whether OSA increases risk of recurrent cardiovascular events remains debated.

So far, multiple studies have sought to demonstrate whether OSA increases the risk of recurrence and death after cardiovascular disease, but the results were inconsistent and the sample sizes of most studies were relatively small. Moreover, as far as we know, there is no study available that evaluates the associations between OSA and serious adverse outcomes in patients with stroke or IHD through meta-analysis. Considering the high prevalence of OSA in those patients and its treatability, we aimed to perform a systematic review and meta-analysis to identify whether OSA increases the risk of recurrence and death after stroke or IHD.

## METHODS

The methodology for this study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>10</sup> Ethical approval was not necessary for this meta-analysis as the results for publication only involved deidentified pooled data from individual studies that have received ethics approval.

## Study Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: English language articles; prospective studies that recruited patients who had been diagnosed with stroke or IHD; the diagnosis of OSA was based on apnea-hypopnea index

**TABLE 1.** Search Strategy: Searching MEDLINE and EMBASE (Ovid SP) on August 25, 2014

Item No.	Searches	Results	Search Type
1	Obstructive sleep apnea.mp.	14048	Advanced
2	Sleep-disordered breathing.mp.	6055	Advanced
3	1 or 2	17295	Advanced
4	cardiovascular disease.mp.	169491	Advanced
5	Ischemic heart disease.mp.	31773	Advanced
6	Myocardial infarction.mp.	204995	Advanced
7	Coronary artery disease.mp.	111634	Advanced
8	Acute coronary syndrome.mp.	23305	Advanced
9	Angina.mp.	76689	Advanced
10	Stroke.mp.	298861	Advanced
11	Cerebrovascular disease.mp.	32945	Advanced
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	590364	Advanced
13	3 and 12	5766	Advanced
14	Limit 13 to (articles with abstracts and original articles)	2906	Advanced

(AHI), which was obtained by polysomnography (AHI is defined as the frequency of apneas and hypopneas/hour of sleep)<sup>1</sup>; follow-up duration of  $\geq 6$  months after stroke or IHD; reporting the results of our interest outcomes, including stroke, IHD, and all-cause or cardiovascular mortality.

### Search Strategy

A systematic search was performed on August 25, 2014 by searching MEDLINE and EMBASE (OvidSP). Details of the search strategy are provided in Table 1. Initially, titles alone were reviewed for suitability. The abstracts of suitable titles were obtained, and these were then reviewed for suitability for full-text retrieval. Data were then extracted as described in the following text from suitable full-text reports. Additional appropriate reports were added when discovered by citation tracking.

### Data Extraction

References were screened and data were extracted independently by 2 authors (FZ and XS) using a predetermined data collection template. To resolve discrepancies about inclusion of studies and interpretation of data, a third investigator (WX) was consulted, and consensus was reached by discussion. The following data were recorded: first author's last name, year of publication, location of study, inclusion and exclusion criteria, sample size, demographic details of patients, follow-up period, and outcomes.

### Validity Assessment

The quality of all included studies was assessed using a modified scoring system, which allowed a total score of 0 to 6 points (6 refers to the highest quality) on the basis of the PRISMA statement.<sup>10</sup> The system allocated 1 point for each of the following: appropriate inclusion and exclusion criteria; diagnosis of stroke, IHD, and all-cause mortality based on accepted clinical criteria; OSA assessed with a standard polysomnography; sample size  $>150$ ; follow-up duration  $>3$  years; adjustments made for age, sex, body mass index, diabetes, hypertension, and smoking.

### Statistical Analyses

Relative risk (RR) was used as the estimate effect of OSA on the risk of stroke, IHD, and all-cause mortality across

studies. Hazard ratio (HR) was directly considered as RR. When a study did not report HR or RR of the outcomes of interest, we calculated the unadjusted RR based on the original data of events by ourselves.

For meta-analysis of stroke, the outcomes included were stroke and transient ischemic attack. For IHD, we included outcomes that were reported as myocardial infarction, angina, revascularization, and acute coronary syndrome. For mortality, outcomes included all-cause mortality and cardiovascular death. In addition, we performed a separate meta-analysis to evaluate the effect of CPAP treatment on adverse outcomes following stroke or IHD in OSA patients.

Data were analyzed within a random-effect framework that takes study heterogeneity into account to generate the pooled RR and 95% confidence interval (CI). The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the  $I^2$  statistic. Potential publication bias was assessed with the Egger test and represented graphically with funnel plots of the natural log of the RR versus its standard error.<sup>11</sup> A 2-sided  $P$  value of  $<0.05$  was judged significant for all analyses. All statistical meta-analyses were done with STATA (version 11; Stata Corp, College Station, TX).

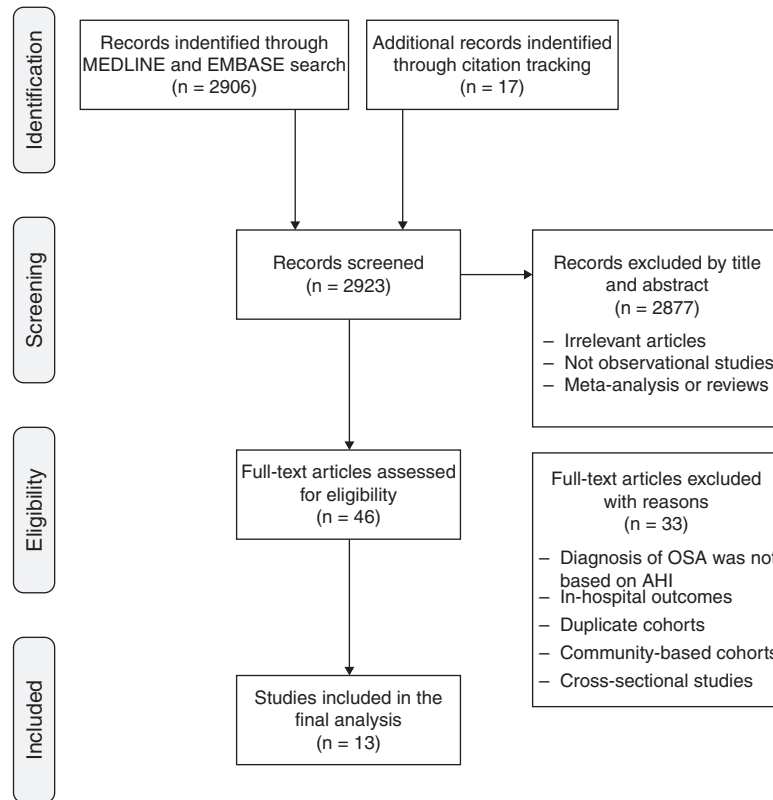
## RESULTS

### Study Selection

From a total of 2906 reports in the initial search, 46 articles met the inclusion criteria and were selected for detailed assessment. Thirty-three studies were further excluded because of studies that did not use AHI to diagnose OSA, studies that investigated in-hospital outcomes, duplicated cohorts, community-based cohort studies, or cross-sectional studies. Finally, a total of 13 studies<sup>12–24</sup> were included in this meta-analysis. Figure 1 shows the study selection process according to the PRISMA statement.<sup>10</sup>

### Study Characteristics

Characteristics of the 13 included studies are summarized in Table 2. Of the 13 hospital-based cohort studies, participants of 6 studies<sup>12,14,17,19–21</sup> were stroke patients and the other 7 studies<sup>13,15,16,18,22–24</sup> included IHD patients. In total, 5 studies<sup>12,14,18,19,22</sup> ( $n = 860$ ) reported the risk of stroke, 6 studies<sup>13,14,16,18,22,24</sup> ( $n = 1083$ ) reported IHD risk, and



**FIGURE 1.** Study selection flow diagram adapted from the PRISMA statement. AHI = apnea-hypopnea index, OSA = obstructive sleep apnea, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

11 studies (n = 1930) reported all-cause mortality<sup>12,14–17,19–23</sup> or cardiovascular death.<sup>18</sup> Six studies scored  $\geq 5$  (relatively high quality), 3 studies scored equal to 4, and 4 studies scored equal to 3 (relatively low quality).

Table 3 presents the results of the associations between OSA and 3 different outcomes from the 13 studies. Most of the studies did not report the adjusted HRs needed

for our meta-analyses. In this scenario, we calculated the unadjusted RR based on the original data. The key inclusion and exclusion criteria of the 13 studies are described in Supplementary Table S1, <http://links.lww.com/MD/A116>. Outcomes were assessed mainly from interviews, hospital discharge registries, death certificates, and medical records.

**TABLE 2.** Characteristics of Included Cohort Studies

Study	Location	Patients	Sample Size	Male %	Mean Age, y	Follow-up, y	Outcomes	Quality Score
Bassetti et al <sup>12</sup>	Switzerland	Stroke	152	67.8	56	5 (mean)	16 Nonfatal stroke/MI and 18 deaths	5
Lee et al <sup>13</sup>	Singapore	IHD	105	98.1	53	1.5	8 Revascularizations and 2 reinfarctions	3
Martinez-Garcia et al <sup>14</sup>	Spain	Stroke	166	59.0	73	7	24 MI/angina, 72 strokes, and 89 deaths	6
Mehra et al <sup>15</sup>	USA	IHD	104	98.1	61	0.5	5 Deaths	4
Nakashima et al <sup>16</sup>	Japan	IHD	272	75.0	68	4 (median)	30 ACS events and 28 deaths	6
Parra et al <sup>17</sup>	Spain	Stroke	161	50.9	72	1.9 (mean)	22 Deaths	4
Peker et al <sup>18</sup>	Sweden	IHD	59	72.9	68	5	13 MI, 6 strokes, and 10 fatal CVD events	4
Rola et al <sup>19</sup>	Poland	Stroke	91	86.8	65	2	15 Stroke/TIA and 6 deaths	3
Sahlin et al <sup>20</sup>	Sweden	Stroke	132	40.9	77	10 (mean)	116 Deaths	5
Turkington et al <sup>21</sup>	UK	Stroke	120	41.7	79	0.5	44 Deaths	3
Valham et al <sup>22</sup>	Sweden	IHD	392	32.7	60	10	47 Strokes, 78 MI, and 80 deaths	6
Won et al <sup>23</sup>	USA	IHD	281	97.5	65	4.1 (mean)	97 Deaths	5*
Yumino et al <sup>24</sup>	Japan	IHD	89	77.5	66	0.6 (mean)	13 Revascularizations and 1 cardiac death	3

ACS = acute coronary syndrome, CVD = cardiovascular disease, IHD = ischemic heart disease, MI = myocardial infarction, TIA = transient ischemic attack.

\*The adjusted risk factors were not clearly disclosed.

**TABLE 3.** Adjusted Risk Factors and Data Extraction of Included Cohort Studies

Study	Risk Factor Adjustment	Exposure vs Control	RR/HR (95% CI)
<b>Stroke</b>			
Bassetti et al <sup>12</sup>	No adjustment	AHI $\geq 30$ vs AHI $< 10$	RR: 1.01 (0.29–3.55)
Martinez-Garcia et al <sup>14</sup>	No adjustment	AHI $\geq 20$ vs AHI $< 20$	RR: 1.90 (1.25–2.87)
Peker et al <sup>18</sup>	No adjustment	AHI $\geq 10$ vs AHI $< 10$	RR: 0.54 (0.07–4.26)
Rola et al <sup>19</sup>	No adjustment	AHI $> 5$ vs AHI $\leq 5$	RR: 1.97 (0.60–6.45)
Valham et al <sup>22</sup>	10 Risk factors*	AHI $\geq 15$ vs AHI $< 5$	HR: 3.56 (1.56–8.16)
<b>IHD</b>			
Lee et al <sup>13</sup>	No adjustment	AHI $\geq 30$ vs AHI $< 30$	RR: 5.55 (1.24–24.86)
Martinez-Garcia et al <sup>14</sup>	No adjustment	AHI $\geq 20$ vs AHI $< 20$	RR: 1.46 (0.66–3.22)
Nakashima et al <sup>16</sup>	7 Risk factors <sup>†</sup>	AHI $\geq 15$ vs AHI $< 15$	HR: 2.30 (1.04–5.13)
Peker et al <sup>18</sup>	No adjustment	AHI $\geq 10$ vs AHI $< 10$	RR: 1.68 (0.64–4.38)
Valham et al <sup>22</sup>	No adjustment	AHI $\geq 5$ vs AHI $< 5$	RR: 1.11 (0.74–1.66)
Yumino et al <sup>24</sup>	No adjustment	AHI $\geq 10$ vs AHI $< 10$	HR: 5.31 (1.19–23.81)
<b>All-cause mortality</b>			
Bassetti et al <sup>12</sup>	No adjustment	AHI $\geq 30$ vs AHI $< 10$	RR: 2.35 (0.75–7.34)
Martinez-Garcia et al <sup>14</sup>	No adjustment	AHI $\geq 20$ vs AHI $< 20$	RR: 1.51 (1.10–2.07)
Mehra et al <sup>15</sup>	No adjustment	AHI $> 10$ vs AHI $< 10$	RR: 2.03 (0.24–17.48)
Nakashima et al <sup>16</sup>	No adjustment	AHI $\geq 15$ vs AHI $< 15$	RR: 1.38 (0.68–2.78)
Parra et al <sup>17</sup>	No adjustment	AHI $\geq 30$ vs AHI $< 30$	RR: 2.58 (1.20–5.52)
Peker et al <sup>18</sup>	No adjustment	AHI $\geq 10$ vs AHI $< 10$	RR: 4.03 (1.31–12.45)
Rola et al <sup>19</sup>	No adjustment	AHI $> 5$ vs AHI $\leq 5$	RR: 0.98 (0.19–5.07)
Sahlin et al <sup>20</sup>	9 Risk factors <sup>‡</sup>	AHI $\geq 15$ vs AHI $< 15$	HR: 1.76 (1.05–2.95)
Turkington et al <sup>21</sup>	No adjustment	AHI $> 10$ vs AHI $< 10$	RR: 1.81 (1.08–3.04)
Valham et al <sup>22</sup>	10 Risk factors*	AHI $\geq 5$ vs AHI $< 5$	HR: 0.99 (0.63–1.60)
Won et al <sup>23</sup>	Patient characteristics (not clear)	AHI $\geq 30$ vs $5 < \text{AHI} < 30$	HR: 1.72 (1.01–2.91)

AHI = apnea-hypopnea index, CI = confidence interval, HR = hazard ratio, IHD = ischemic heart disease, RR = relative risk.

\* Age, sex, body mass index, diabetes, hypertension, current smoking, atrial fibrillation, left ventricular function, coronary artery intervention, and previous stroke/transient ischemic attack.

† Age, sex, body mass index, diabetes, hypertension, hypercholesterolemia, and current smoking.

‡ Age, sex, body mass index, diabetes, hypertension, current smoking, atrial fibrillation, Mini-Mental State Examination score, and Barthel index.

### OSA and the Risk of Stroke

Five studies were included in the meta-analysis for the associations of OSA with the risk of stroke. Of these, 3 studies<sup>12,14,19</sup> were conducted in stroke patients and 2 studies<sup>18,22</sup> were conducted in IHD patients. The RRs for the association varied from 0.54 to 3.57 across studies. Overall, OSA was significantly associated with the risk of stroke in patients with stroke or IHD (RR = 1.94; 95% CI, 1.29–2.92;  $P = .001$ ). There was no evidence of significant between-study heterogeneity ( $I^2 = 13.2\%$ ,  $P = .33$ , Figure 2).

Subgroup analysis by patient type found a significant RR, 1.80 (95% CI, 1.24–2.62;  $P = .002$ ) in stroke patients, with no evidence of statistical heterogeneity ( $I^2 = 0.0\%$ ,  $P = .64$ , Figure 2).

### OSA and the Risk of IHD

Five studies<sup>13,16,18,22,24</sup> in IHD patients and 1 study<sup>14</sup> in stroke patients were included in the pooled analysis. OSA was also found to be a significant risk factor for IHD in patients with IHD or stroke (RR = 1.83; 95% CI, 1.15–2.93;  $P = .011$ ). No evidence of significant between-study heterogeneity was found ( $I^2 = 44.2\%$ ,  $P = .11$ , Figure 3).

When only samples from IHD patients were included, there was positive evidence for association between OSA and recurrent risk of IHD (RR = 2.06; 95% CI, 1.13–3.77;

$P = .02$ ), with moderate but nonsignificant heterogeneity ( $I^2 = 55.3\%$ ,  $P = .062$ , Figure 3).

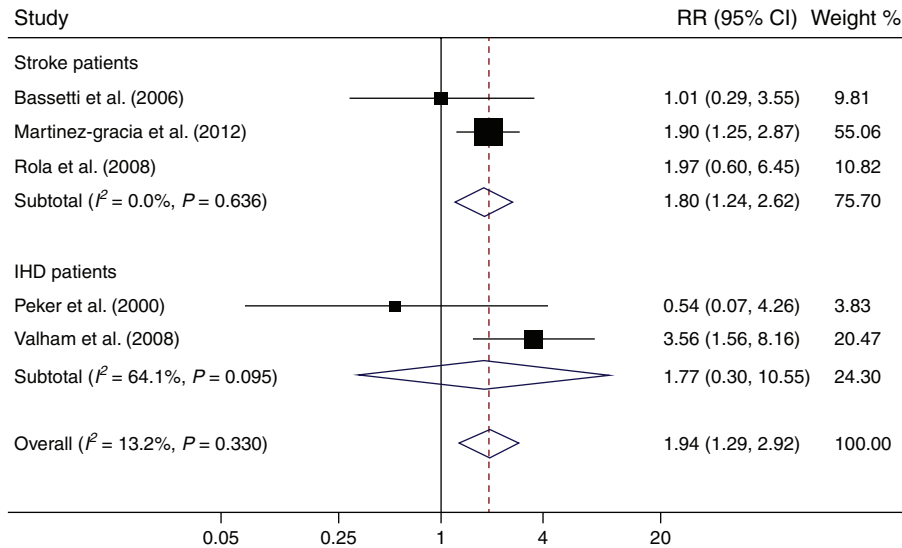
### OSA and All-Cause Mortality

Eleven studies were included in the meta-analysis, 6 were<sup>12,14,17,19–21</sup> in stroke patients and 5 were<sup>15,16,18,22,23</sup> in IHD patients. The total number of the patients was 1930 with 515 deaths. Overall, OSA significantly increased the all-cause mortality (RR = 1.59; 95% CI, 1.33–1.89;  $P < .001$ ). There was no evidence of heterogeneity across studies ( $I^2 = 0.0\%$ ,  $P = .47$ , Figure 4).

Subgroup analysis showed that the association was significant in stroke patients (RR = 1.69; 95% CI, 1.36–2.12;  $P < .001$ ), with no evidence of heterogeneity ( $I^2 = 0.0\%$ ,  $P = .78$ ). However, the association did not achieve significance in IHD patients (RR = 1.50; 95% CI, 0.99–2.27;  $P = .053$ , Figure 4).

### Effect of CPAP Treatment on Adverse Outcomes

Three studies<sup>14,16,23</sup> reported the specified results of outcomes by CPAP treatment in OSA patients and included in the meta-analysis. Supplementary Table S2, <http://links.lww.com/MD/A116> shows the extracted data from the 3 studies. As shown in Figure 5, the treatment of OSA by CPAP in patients with stroke or IHD would significantly reduce the risk of



**FIGURE 2.** Meta-analysis of OSA and associated risk of stroke in patients with stroke or IHD. Squares represent point estimates for effect size expressed as a RR with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, IHD = ischemic heart disease, OSA = obstructive sleep apnea, RR = relative risk.

adverse outcomes (RR = 0.41; 95% CI, 0.25–0.66;  $P < .001$ ), without heterogeneity ( $I^2 = 0.0\%$ ,  $P = .93$ ).

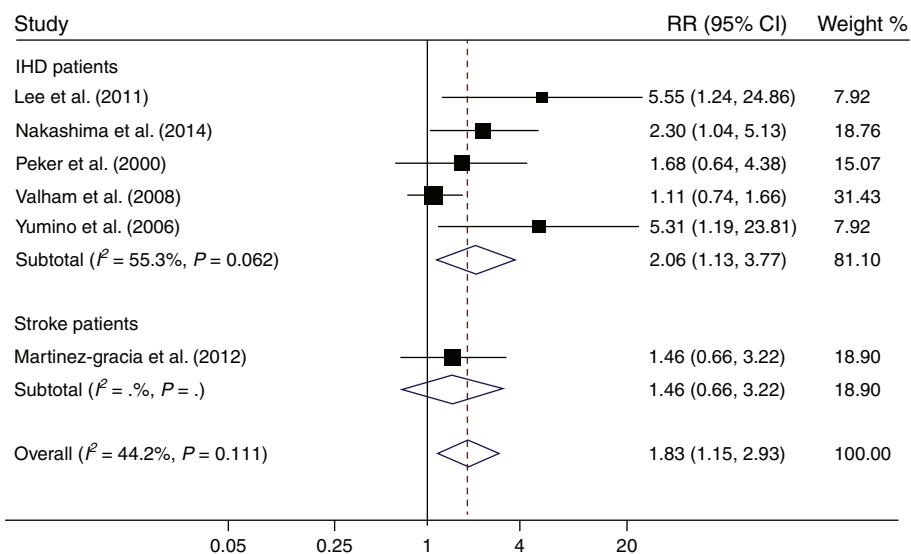
**Sensitivity Analyses**

To assess the effect of variations in quality, as well as possible sources of heterogeneity, a number of sensitivity analyses were conducted. Table 4 presents the results of sensitivity analyses according to various inclusion criteria. Overall, the pooled risk estimates did not materially change in the sensitive analyses for the outcomes of stroke and all-cause mortality. The pooled RRs for IHD were no longer significant in the analyses restricting to studies that have a sample size >150, follow-up duration >3 years, and quality score  $\geq 4$ .

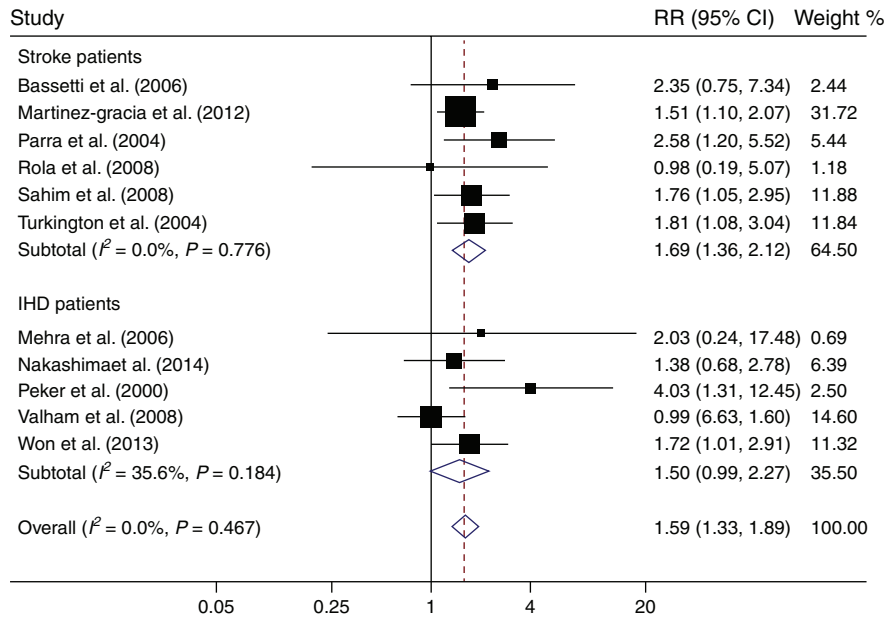
When excluding the study conducted by Valham et al<sup>22</sup> from the analyses, the between-study heterogeneities were significantly reduced for the outcomes of IHD (from 44.2% to 3.2%) and stroke (from 13.2% to 0.0%, Table 4).

**Publication Bias**

There was no evidence of publication bias on the basis of either visual inspection of the funnel plots (Supplementary Figures S1 and S2, <http://links.lww.com/MD/A116>) or Egger test for the outcomes of stroke and all-cause mortality ( $P = 0.51$  and  $P = 0.26$ , respectively). However, funnel plot (Supplementary Figure S3, <http://links.lww.com/MD/A116>) and Egger test suggested the presence of publication bias for



**FIGURE 3.** Meta-analysis of OSA and associated risk of IHD in patients with IHD or stroke. Squares represent point estimates for effect size expressed as a RR with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, IHD = ischemic heart disease, OSA = obstructive sleep apnea, RR = relative risk.



**FIGURE 4.** Meta-analysis of OSA and all-cause mortality in patients with stroke or IHD. Squares represent point estimates for effect size expressed as a RR with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, IHD = ischemic heart disease, OSA = obstructive sleep apnea, RR = relative risk.

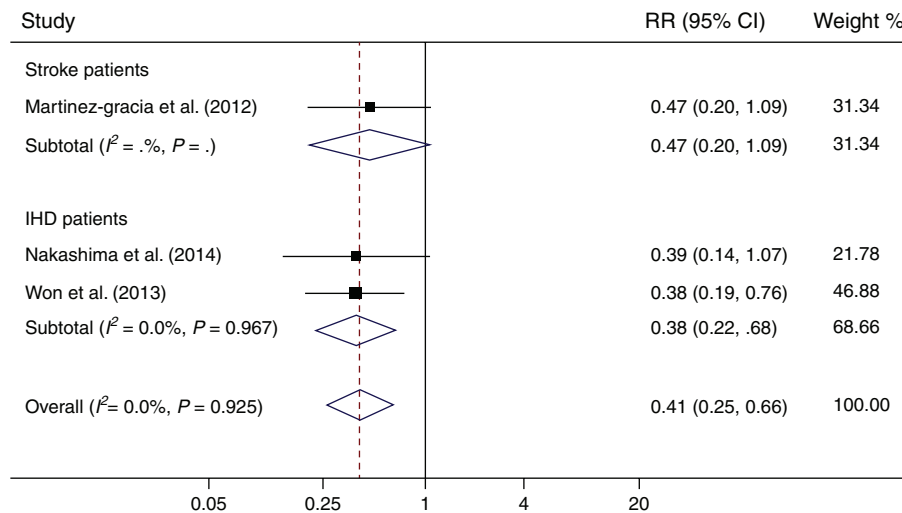
the outcome of IHD ( $P = .006$ ). Contour-enhanced funnel plot indicated that 3 supposed missing studies were in areas of statistical nonsignificance ( $P > 0.05$ ) and relative risk  $< 1$  (Supplementary Figure S4, <http://links.lww.com/MD/A116>). This suggests that the asymmetry is likely because of publication bias.

**DISCUSSION**

The results of the present meta-analysis demonstrated that OSA is associated with a significant increase in the risk of stroke, IHD, and all-cause mortality among patients with stroke

or IHD. As OSA affects approximately 60% to 70% of the cardiovascular patients,<sup>6,7</sup> its impact on cardiovascular burden is likely to be substantial. Our results suggest that OSA should be considered as a potential treatment target that might improve outcome and survival following stroke or IHD.

Three previous meta-analyses were performed to evaluate the association between OSA and cardiovascular risk, and the results were consistent. In the general population, OSA was significantly associated with stroke but not with IHD.<sup>3,25,26</sup> However, to the best of our knowledge, there is no meta-analysis that evaluates the associations between OSA and



**FIGURE 5.** Meta-analysis of the effect of CPAP treatment on adverse outcomes following stroke or IHD in OSA patients. Squares represent point estimates for effect size expressed as a RR with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% CIs. CI = confidence interval, CPAP = continuous positive airway pressure, IHD = ischemic heart disease, OSA = obstructive sleep apnea, RR = relative risk.

**TABLE 4.** Results of Sensitivity Analyses According to Various Inclusion Criteria

Inclusion Criteria	Stroke			IHD			All-Cause Mortality		
	N	RR (95% CI)	I <sup>2</sup> (%)	n	RR (95% CI)	I <sup>2</sup> (%)	n	RR (95% CI)	I <sup>2</sup> (%)
Total	5	1.94 (1.29–2.92)	13.2	6	1.83 (1.15–2.93)	44.2	11	1.59 (1.33–1.89)	0.0
Moderate-to-severe OSA (Exposure, AHI ≥15)	3	2.06 (1.21–3.50)	34.7	3	2.15 (1.18–3.94)	19.1	6	1.66 (1.34–2.06)	0.0
Sample size >150	3	2.06 (1.21–3.50)	34.7	3	1.38 (0.92–2.08)	23.9	6	1.50 (1.18–1.90)	15.1
Follow-up duration >3, y	4	1.89 (1.08–3.28)	34.9	4	1.35 (0.99–1.84)	0.0	7	1.53 (1.21–1.93)	17.6
Quality score ≥4	4	1.89 (1.08–3.28)	34.9	4	1.35 (0.99–1.84)	0.0	9	1.59 (1.28–1.97)	12.2
Excluding Valham et al <sup>22</sup>	4	1.73 (1.20–2.51)	0.0	5	2.18 (1.39–3.42)	3.2	10	1.72 (1.42–2.08)	0.0

AHI = apnea-hypopnea index, CI = confidence interval, IHD = ischemic heart disease, OSA = obstructive sleep apnea, RR = relative risk.

serious adverse outcomes following stroke or IHD in terms of recurrent vascular events and all-cause mortality. Although previous observational studies of CPAP in general OSA populations reported statistically significant reductions in cardiovascular risk associated with CPAP compared with no CPAP,<sup>4,5</sup> screening all participants may not be cost-effective given the costs of polysomnography. Taking into account higher prevalence of OSA and higher risk of cardiovascular events, it is rational to believe that screening for OSA in cardiovascular patients is more cost-effective.<sup>27</sup>

The mechanisms behind the increased risk of cardiovascular events in patients with OSA are still uncertain. A scientific statement, published by the American Heart Association/American College of Cardiology, indicated following 9 potential mechanisms at play: sympathetic activation, cardiovascular variability, vasoactive substances, inflammation, oxidative stress, endothelial dysfunction, insulin resistance, thrombosis, and intrathoracic pressure changes.<sup>1</sup> A recent review by Kohler and Stradling<sup>28</sup> pointed out 3 biological mechanisms underlying the association of OSA with cardiovascular disease: intermittent hypoxia leading to increased oxidative stress, systemic inflammation, and sympathetic activity; intrathoracic pressure changes leading to excessive mechanical stress on the heart and large artery walls; and arousal-induced reflex sympathetic activation with resultant repetitive blood-pressure rises.

Based on this systematic review and meta-analysis, OSA could be identified as a risk factor for recurrence and mortality following vascular events, and treatment of OSA by CPAP would significantly reduce the risk of adverse outcomes. However, few randomized-controlled trials (RCTs) evaluated the effect of CPAP on recurrence and mortality among cardiovascular patients. Our literature review identified only 1 small RCT (n = 126) evaluating the effect of CPAP on cardiovascular risk in stroke patients. No significant improvement in cardiovascular mortality was reported at 24 months (0% in the CPAP group vs 4.3% in the control group, *P* = .161).<sup>29</sup> More RCTs are needed to determine the effect of CPAP on the risk of recurrent cardiovascular events after stroke or IHD. Given the relatively low enrollment and completion rates, no single center is likely to recruit a large enough sample. Therefore, a large-scale, multicenter trial may be the only way to find out whether CPAP helps these patients.

The major advantages of this meta-analysis included the prospective cohort studies, enlarged sample sizes, the robust results from sensitivity analysis, and no significant between-study heterogeneity. However, there are some limitations that should be noted. First, most RRs for meta-analyses were calculated by us and not adjusted for traditional cardiovascular

risk factors because the original studies did not report the adjusted estimates. Thus, we acknowledge the possibility that confounding could affect the results. Second, our systematic review was limited to English-language studies only, which can introduce selection bias. A relevant article in Chinese identified from the published Chinese literature was not included in this study.<sup>30</sup> We also cannot rule out the possibility that there are other relevant articles published in languages other than English or Chinese. However, we consider that the possibility of selection bias is reduced by the relatively large number of studies available in English. In addition, previous studies have demonstrated that excluding studies published in languages other than English has generally little effect on summary effect estimates.<sup>31,32</sup> Third, the ranges of AHI among both exposure and control groups are inconsistent across studies. Originally, we planned to conduct separate meta-analyses for the associations between OSA severity (ie, mild, moderate, and severe OSA) and outcomes. However, most studies did not report the specified results according to OSA categories because of small sample size. Similarly, the limitation has also been found in other meta-analyses.<sup>3,26,33</sup> We perform sensitivity analyses to solve this limitation, at least to a certain degree. In the analyses restricting to studies that have AHI ≥15 in exposure groups, the pooled risk estimates did not materially change. Fourth, all of the included studies were hospital-based, which may lead to selection bias and limit the generalization of the findings. Finally, as with any meta-analyses, publication bias remains a threat to the validity of our results.

In summary, based on this systematic review and meta-analysis, we suggest that OSA may be a significant predictor of serious adverse outcomes following stroke or IHD in terms of recurrent vascular events and all-cause mortality. More high-quality studies are needed to determine if better treatment of OSA leads to fewer recurrent vascular events in stroke or IHD patients, especially a large-scale, multicenter RCT.

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