Association of obstructive sleep apnea with cardiovascular outcomes after percutaneous coronary intervention

A systematic review and meta-analysis

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Abstract

The relationship between obstructive sleep apnea (OSA) and adverse cardiovascular outcomes in patients undergoing percutaneous coronary intervention (PCI) remains unclear. We performed a systematic review and meta-analysis to assess the impact of OSA on subsequent cardiovascular events after PCI.

We searched the PubMed, EMBASE, and Cochrane library from their inceptions to August 5, 2017. We included cohort studies that described the association between OSA (based on apnea-hypopnea index) and cardiovascular outcomes after PCI with stenting. The primary endpoint was major adverse cardiovascular event (MACE), including all-cause or cardiovascular death, myocardial infarction, stroke, repeat revascularization, or heart failure. Outcomes data were pooled using random effects models and heterogeneity was assessed with the I^2 statistic.

We identified 9 studies with 2755 participants. The prevalence of OSA in patients treated with PCI ranged from 35.3% to 61.8%. OSA was associated with increased risk of MACE after PCI (pooled risk ratio [RR] 1.96, 95% confidence interval [CI]: 1.36–2.81, $P < .001$, $I^2 = 54\%$). Between-study heterogeneity was partially explained by sample size (2 studies with ≤100 participants; RR 9.12, 95% CI: 2.69–31.00, $I^2 = 0\%$ vs 7 studies with >100 participants; RR 1.64, 95% CI: 1.23–2.18, $I^2 = 35\%$). Moreover, the presence of OSA significantly increased the incidence of all-cause death (4 studies), cardiovascular death (4 studies), and repeat revascularization (7 studies) in patients undergoing PCI.

Patients with OSA are at greater risk of subsequent cardiovascular events after PCI. Whether treatment of OSA prevents such events warrants further investigation.

Abbreviations: ACS = acute coronary syndrome, AHI = apnea-hypopnea index, CAD = coronary artery disease, CI = confidence interval, CPAP = continuous positive airway pressure, DES = drug-eluting stent, HR = hazard ratio, MACE = major adverse cardiovascular event, MI = myocardial infarction, OSA = obstructive sleep apnea, PCI = percutaneous coronary intervention, RR = risk ratio.

Keywords: coronary artery disease, meta-analysis, obstructive sleep apnea, percutaneous coronary intervention

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1. Introduction

Obstructive sleep apnea (OSA) is an increasingly common chronic disorder in adults.[1] Compared to the general population, OSA occurs more often in patients with coronary artery disease (CAD), with a reported prevalence of 38% to 65%.[2] Emerging evidence indicates OSA initiates and exacerbates coronary atherosclerosis[3,4] and is associated with higher risk of subsequent cardiovascular events in patients with established CAD.[5,6]

Percutaneous coronary intervention (PCI) is nowadays part of standard therapy in patients with symptomatic CAD.[7] However, the long-term cardiovascular outcomes after PCI remain suboptimal despite optimal medical therapy to manage traditional risk factors.[8] In the past decade, multiple observational studies,[5,6,9–15] including the recently published multicenter sleep and stent study,[15] have examined whether presence of OSA significantly increased risk of recurrent cardiovascular events in patients treated with PCI, but the results are inconsistent and the interpretation of these results remains disputable given variability in sample size, follow-up duration, and adjustment for potential confounders (coexisting clinical variables) across studies. Hence, we conducted a systematic review and meta-analysis of cohort studies to assess the impact of OSA on subsequent cardiovascular outcomes after PCI.

2. Methods

2.1. Search strategies

This meta-analysis was conducted in accordance to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[16] We systematically searched the PubMed, EMBASE, and Cochrane library from their inceptions to August 5, 2017 for studies describing the association between OSA and cardiovascular outcomes after PCI. We used Medical Subject Heading terms "Sleep Apnea Syndromes," "Percutaneous Coronary Intervention," "Myocardial Ischemia," and related text words including sleep apnea, stent, and coronary disease, without language restrictions. Reference lists of all identified publications and relevant review articles were further checked manually for potential citations. An example search strategy is presented in Supplemental Table 1, http://links.lww.com/MD/C230.

2.2. Study selection and eligibility criteria

Two authors (XW and JYF, both cardiologists) assessed the eligibility of articles by initially screening the titles and abstracts. Articles were considered for inclusion if they reported original data on clinical outcomes in patients with OSA and CAD and/or receiving PCI. Full-text articles were subsequently reviewed in duplicate. We only selected cohort studies (retrospective cohort or prospective cohort) that recruited patients undergoing PCI with stenting, with a comparison between untreated OSA versus controls (no OSA or with varying degrees of OSA severity). In case of studies comparing treated OSA with untreated OSA and to those without OSA, only untreated OSA and no OSA (control) cohorts were included in this study. The diagnosis of OSA was based on apnea-hypopnea index (AHI) obtained by standardized polysomnography or portable diagnostic devices. Included studies had to have a longitudinal follow-up duration of >6 months. The primary outcome of interest for inclusion was major adverse cardiovascular events (MACEs). The following exclusion criteria were used: no PCI or stent information; OSA diagnosis was not based on AHI; studies that did not specify exclusion of patients with predominantly central sleep apnea; studies comparing treated OSA versus untreated OSA; and cardiovascular outcomes not reported or no long-term follow-up. Any disagreement was resolved by consensus through referral to a 3rd reviewer (SPN). An ethical approval was not necessary since meta-analysis was based on secondary data.

2.3. Data extraction and validity assessment

Data extraction was performed by 2 independent reviewers (XW and JYF) using a prespecified standardized form, and verified by a senior author (SPN). All discrepancies were resolved by consensus. We also contacted authors for missing data. The following study information were recorded: study design, location, date, sample size, demographic characteristics, procedural characteristics, methods and timing of OSA assessment, duration and completeness of follow-up, cardiovascular outcomes, and adjustments of potential confounding factors. The definitions of exposure (OSA) and control groups were based on AHI cut-points in each study.

The quality of included studies was evaluated independently by 2 authors (XW and JYF) using the Newcastle-Ottawa Scale for cohort studies.[17] A quality score was calculated according to a maximum of 1 star for each item upon selection (4 items:

representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and demonstration that outcome was not present at study start), comparability (2 items: controls for the most important factor and any additional factor), and outcome (3 items: assessment, duration, and adequacy of follow-up) categories.

The primary endpoint was MACE, defined as a composite of all-cause or cardiovascular death, myocardial infarction (MI), stroke, repeat revascularization, or heart failure. Secondary endpoints included all-cause death, cardiovascular death, MI, stroke, and repeat revascularization. Definitions of events were in accordance to guidelines during each study period, although the timing of definitions varies among studies. Repeat revascularization was generally defined as unplanned or target vessel revascularization. If these data were not recorded, data on any repeat revascularization were used. Endpoints were assessed at the longest follow-up. The quality of each outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[18]

2.4. Data synthesis and analysis

We used risk ratio (RR) as the effect estimate of OSA on the risk of cardiovascular events after PCI. In general, we collected multivariable-adjusted hazard ratio (HR) or RR from original studies. HR was directly considered as RR. In case of unreported HR or RR of the outcomes of interest, we calculated unadjusted RR using crude values. We pooled RR with 95% confidence interval (CI) for MACE and significant secondary outcomes by random effects model (DerSimonian-Laird), which incorporates between-study heterogeneity. The Cochran Q test (at a significance level of $P < .10$) and the I^2 statistic were used to examine statistical heterogeneity across studies. For primary outcome, we performed prespecified sensitivity analysis by excluding retrospective cohort, studies with unadjusted data, or low-to-moderate quality studies, respectively. Post hoc sensitivity analysis was conducted based on drug-eluting stent (DES) use, AHI definition, sample size, or follow-up duration. Publication bias was assessed by funnel plots, Egger test, and trim-and-fill analysis. All analyses were performed with Cochrane Review Manager software (version 5.3) and Stata version 11.2 (StataCorp LP, College Station, TX). Unless otherwise indicated, a 2-sided P value $< .05$ was considered statistically significant.

3. Results

3.1. Study selection and characteristics

Our search yielded 4653 citations. By first screen, 26 studies were retained for further review. We subsequently excluded 17 studies, of which 7 studies included patients with CAD but no PCI or stent information was specified, and 4 studies did not report cardiovascular events or long-term (>6 months) follow-up. Other reasons for study exclusion are presented in Fig. 1.

Therefore, a total of 9 studies with 2755 participants were included in this meta-analysis.[5,6,9–15] The prevalence of OSA ranged from 35.3% to 61.8%. Characteristics of the studies are listed in Tables 1 and 2. Studies were published in the past 10 years. Eight studies were prospective cohorts,[5,6,9–12,14,15] and 1 study was retrospective cohort.[13] Seven studies enrolled mostly acute coronary syndrome (ACS) patients with PCI,[5,6,9,11,13–15] and 2 studies enrolled only MI patients undergoing primary PCI.[10,12] Five studies specified DES use in most patients,[9,11,13–15] whereas 4
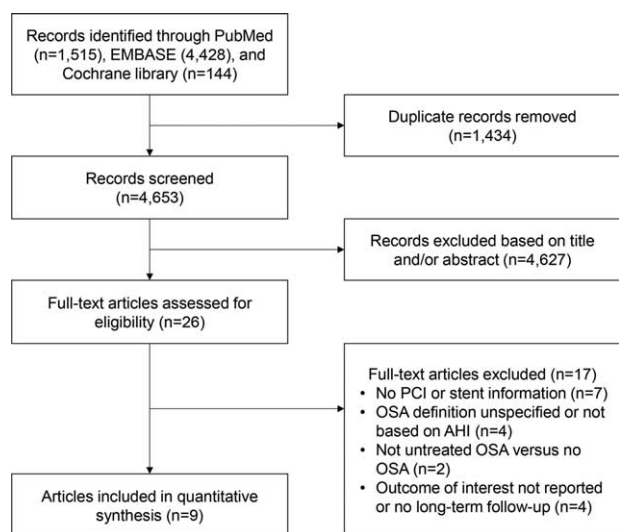
Figure 1. Flow chart of the study selection process for meta-analysis. OSA = obstructive sleep apnea, PCI = percutaneous coronary intervention.

studies used bare-metal stents,[5,6] endothelial progenitor cell capturing stents,[10] or did not indicate stent information.[12] OSA was assessed primarily by overnight polysomnography in 2 studies,[12,13] and by validated portable diagnostic devices in 7 studies.[5,6,9–11,14,15] Almost all sleep studies were done within 1 month after PCI or admission,[5,6,9–12,14,15] except 1 retrospective study done within 1 month before or after PCI.[13]

The definition of OSA was based on standardized assessment of AHI in all studies, with AHI≥15 as cut-off value in most studies.[11–15] Two studies compared treated OSA with untreated OSA and to those without OSA (control), and only untreated OSA and control cohorts were included in this meta-analysis.[12,13] The median follow-up duration was from 227 days to 5.6 years, and a mild proportion of patients were lost to follow-up (up to 4.9%). All studies had no treatments for OSA during this period. To be noted, most of the studies reported adjusted

risk estimates for the primary endpoint, but some studies did not adjust for all or part of potential confounding factors, including age, sex, body mass index, hypercholesterolemia, hypertension, diabetes, and smoking, thus contributing to risk of bias. The quality scores of studies are shown in Supplemental Table 2, http://links.lww.com/MD/C230.

3.2. OSA and MACE after PCI

Overall, OSA was significantly associated with increased risk of MACE after PCI (RR 1.96, 95% CI: 1.36–2.81, $P < .001$) (Fig. 2). There was evidence of statistical heterogeneity for the composite endpoint (Q statistic $P = .02$; $I^2 = 54\%$). Subgroup analysis according to sample size showed that the pooled RR of 2 studies with ≤100 patients (RR 9.12, 95% CI: 2.69–31.00, $I^2 = 0\%$) was greater than that of 7 studies with >100 patients (RR 1.64, 95% CI: 1.23–2.18, $I^2 = 35\%$), and the heterogeneity was attenuated in both subgroups (Supplemental Fig. 1, http://links.lww.com/MD/C230). The increased risk of MACE remained significant in 7 studies with adjusted results (RR 2.30, 95% CI: 1.56–3.37, $I^2 = 36\%$), but was not significant in 2 studies without adjustment (RR 1.11, 95% CI: 0.80–1.54, $I^2 = 0\%$) (Supplemental Fig. 2, http://links.lww.com/MD/C230). Noteworthy, the risk estimate of MACE without the large multicenter sleep and stent study (2.22) was consistent with the overall effect from all studies (1.96), but the 95% CI became narrower with the addition of the sleep and stent study (1.38–3.57 to 1.36–2.81) (Supplemental Fig. 3, http://links.lww.com/MD/C230).

We further performed sensitivity analyses to explore the effect of variations in quality and potential sources of heterogeneity (Table 3). We excluded those studies with low-to-moderate quality (Newcastle-Ottawa Scale score < median value) and found no change in the significance of effect size and between-study heterogeneity reduced significantly (I^2 from 54% to 0%). We also evaluated the effects of excluding studies with retrospective cohort, unadjusted values, a cutoff value of other than AHI ≥15, sample size ≤100, follow-up duration ≤1 year, as well as 4 studies that used other stent types or did not indicate stent information. All the analysis did not change the statistical

Table 1

Study design, patients demographics, and procedural characteristics.

Source	Study design, location, y	Number of participants	Primary CAD diagnosis, %	Age, mean, y	Men, %	BMI, mean	Stenting information, %	OSA assessment	Timing of sleep study
Yumino et al,[5] 2007	Prospective cohort, single-center in Japan, NR	89	ACS, 100%	66	77.5	24.1	BMS, 100%	Portable diagnostic device	7–14 d after PCI
Meng et al,[9] 2009	Prospective cohort, single-center in China, 2008	123	ACS, 100%	66.7	69.1	23.7	DES, 100%	Portable diagnostic device	Within 7 d after PCI
Lee et al,[10] 2011	Prospective cohort, single-center in Singapore, 2007–2008	105	STEMI, 100%	52.7	98.1	24.9	Endothelial progenitor cell capturing stents, 70.5%; BMS, 27.6%; DES, 1.9%	Portable diagnostic device	Between day 2 and 5 after PCI
Loo et al,[11] 2014	Prospective cohort, single-center in Singapore, 2011–2012	68	ACS, 100%	54.2	86.8	25.5	DES, 66.2%	Portable diagnostic device	14 d (median) after PCI
Nakashima et al,[12] 2015	Prospective cohort, single-center in Japan, 2003–2009	216	AMI, 100%	67.7	75.0	NR	Stent, 89.7%	Polysomnograph	Between 14 and 21 d after the 1st admission
Wu et al,[13] 2015	Retrospective cohort, single-center in China, 2002–2012	262	ACS, 69.2%	56.3	84.1	Median OSA: 29.5 Con: 27.7	DES, 100%	Polysomnograph 72.1%, Portable diagnostic device 27.9%	Within 1 mo before or after PCI
Mazaki et al,[6] 2016	Prospective cohort, single-center in Japan, 2005–2008	241	ACS, 100%	63.5	76.8	25.1	BMS, 100%	Portable diagnostic device	6 d (median) after ACS onset
Zhang et al,[14] 2016	Prospective cohort, single-center in China, 2012–2014	340	ACS, 90.0%	64.7	73.2	24.9	DES, 100%	Portable diagnostic device	7–10 d after PCI
Sleep and Stent,[15] 2016	Prospective cohort, 8 centers in Asia and South America, 2011–2014	1311	ACS, 68.5%	58.2	85.2	25.7	DES, 80.1%; BMS, 7.0%; BVS, 6.3%	Portable diagnostic device	Within 7 d after PCI

ACS = acute coronary syndrome, AMI = acute myocardial infarction, BMI = body mass index, BMS = bare-metal stent, BVS = bioresorbable vascular scaffold, CAD = coronary artery disease, DES = drug-eluting stent, NR = not reported, OSA = obstructive sleep apnea, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction.

Table 2

**Study groups, outcomes, results, and risk of bias.**

Source	Exposure	Control	Follow-up	Loss to follow-up, %	Definitions of primary outcome (MACE)	Results	Confounders included in adjusted analysis	Newcastle–Ottawa Scale Score
Yumino et al,[5] 2007	AHI ≥ 10	AHI < 10	227 d (mean)	0	Cardiac death, reinfarction. or target vessel revascularization	Adjusted HR, 11.61 (2.17–62.24)	Age, BMI, hypertension, hypercholesterolemia, diabetes mellitus, ejection fraction, high-sensitivity C-reactive protein, and Epworth Sleepiness Scale	7
Meng et al,[9] 2009	AHI ≥ 5	AHI < 5	1 y	0	Cardiac death, target vessel revascularization, heart failure, or stroke	Unadjusted RR, 1.66 (0.63–4.37)	NR	6
Lee et al,[10] 2011	AHI ≥ 30	AHI < 30	18 mo	0	Death, reinfarction, stroke, unplanned target vessel revascularization, and heart failure requiring hospitalization	Adjusted HR, 5.36 (1.01–28.53)	Age, BMI	8
Loo et al,[11] 2014	AHI ≥ 15	AHI < 15	20 mo (median)	0	Cardiac death, MI, stroke, unplanned revascularization, and hospitalization for heart failure	Adjusted HR, 6.95 (1.17–41.4)	Age, gender, STEMI presentations, hypertension, smoking, and BMI	9
Nakashima et al,[12] 2015	AHI ≥ 15	AHI < 15	4 y (median)	4.9	Cardiac death, ACS recurrence, and re-admission for heart failure	Adjusted HR, 2.20 (1.09–4.24)	Hypercholesterolemia, hypertension, diabetes, current smoking, BMI ≥25 kg/m², age ≥75 y, and male gender	9
Wu et al,[13] 2015	AHI ≥ 15	AHI 5–14.9	4.8 y (median)	1.5	Death, nonfatal MI, repeat revascularization, stent thrombosis, or stroke	Unadjusted RR, 1.05 (0.74–1.49)	NR	7
Mazaki et al,[6] 2016	AHI ≥ 5	AHI < 5	5.6 y (median)	0	All-cause death, recurrence of ACS, nonfatal stroke, and hospital admission for congestive heart failure	Adjusted HR, 2.28 (1.06–4.92)	Age, current smokers, ejection fraction, mean SaO₂, minimum SaO₂, use of β-blockers, and use of statins	9
Zhang et al,[14] 2016	AHI ≥ 15	AHI < 15	2 y (median)	0	Cardiac death, MI, and/or target vessel revascularization	Adjusted HR, 1.96 (1.04–3.72)	Ejection fraction	8
Sleep and Stent,[15] 2016	AHI ≥ 15	AHI < 15	1.9 y (median)	2.0	Cardiovascular mortality, nonfatal MI, nonfatal stroke, and unplanned revascularization	Adjusted HR, 1.57 (1.10–2.24)	Age, sex, ethnicity, BMI, hypertension, and diabetes mellitus	9

ACS = acute coronary syndrome, AHI = apnea-hypopnea index, BMI = body mass index, HR = hazard ratio, MACE = major adverse cardiovascular events, MI = myocardial infarction, NR = not reported, RR = risk ratio, STEMI = ST-segment elevation myocardial infarction.

significance or direction of effect for the primary endpoint, and showed slight decrease of heterogeneity. It should be noted that the quality of primary outcome was low based on GRADE system (Supplemental Table 3, http://links.lww.com/MD/C230), so the result should be interpreted with caution.

The funnel plot for the outcome of MACE was asymmetrical indicating possibility of publication bias, and it was suggested by Egger test ($P=.002$). When we used the trim-and-fill analysis to quantify the potential effect of small-study bias, addition of hypothetical missing studies reduced the pooled RR to 1.55 (95% CI: 1.07–2.24, $P=.02$) in random effects model but continued to show a significant association between OSA and MACE (Supplemental Figure 4, http://links.lww.com/MD/C230).
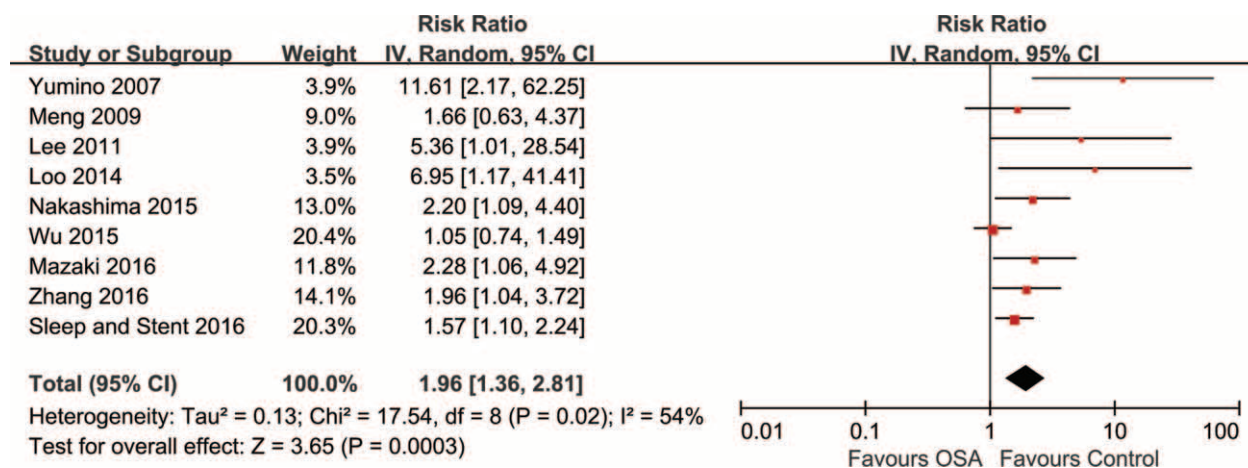
Figure 2. Risk estimates for MACE. Forest plot displays the risk ratio with 95% CI for MACE in patients with OSA compared to control. The diamond indicates the point estimate, and the left and right end of the line indicate the 95% CI. CI = confidence interval, IV = inverse variance, MACE = major adverse cardiovascular events, OSA = obstructive sleep apnea.

Table 3

Sensitivity analysis for MACE.

Included studies	No of studies	No of participants	RR (95% CI)	P	I^2, %	P value for heterogeneity
Overall	9	2755	1.96 (1.36–2.81)	<.001	54	.02
Prospective cohort	8	2493	2.16 (1.54–3.01)	<.001	26	.22
Adjusted for confounders	7	2370	2.30 (1.56–3.37)	<.001	36	.15
High-quality study*	6	2281	1.89 (1.46–2.46)	<.001	0	.42
OSA defined as AHI ≥15	5	2197	1.62 (1.12–2.35)	.01	54	.07
Sample size >100	7	2598	1.64 (1.23–2.18)	<.001	35	.16
Duration of follow-up >1 y	7	2543	1.78 (1.26–2.53)	.001	50	.06
DES	5	2104	1.52 (1.07–2.17)	.02	45	.12

CI = confidence interval, DES = drug-eluting stent, MACE = major adverse cardiovascular events, RR = risk ratio.
* Defined as Newcastle-Ottava Scale score ≥8 (median value of all studies).

3.3. OSA and individual cardiovascular events after PCI

In studies reporting outcomes of death, OSA was found to significantly increase the risk of all-cause death (4 studies with 1919 participants; RR 1.70, 95% CI: 1.05–2.77, $I^2 = 0\%$) (Fig. 3A)[6,10,13,15] and cardiovascular death (4 studies with 1863 participants; RR 2.23, 95% CI: 1.08–4.59, $I^2 = 0\%$) (Fig. 3B)[5,9,14,15] in the pooled analysis, with no evidence of statistical heterogeneity.

We also included 7 studies (2298 participants) with data on repeat revascularization and found higher risk in patients with OSA (RR 1.54, 95% CI: 1.17–2.02, $I^2 = 0\%$) (Fig. 4C), with no evidence of heterogeneity.[5,9–11,13–15] However, there were no significant difference for outcomes of MI and stroke (Fig. 4A and B). The quality of each individual outcome was shown in Supplemental Table 3, http://links.lww.com/MD/C230.

4. Discussion

Our meta-analysis demonstrated that OSA was associated with a pooled 2-fold risk of recurrent cardiovascular events after PCI, which supports existing evidence including the multicenter sleep and stent study.[15] Between-study heterogeneity was partially explained by sample size and study quality based on Newcastle-Ottava Scale score or whether adjustment for confounders was performed. Our estimates remained robust to a variety of sensitivity analysis. Furthermore, the presence of OSA significantly increased the incidence of all-cause death, cardiovascular death, and repeat revascularization in patients undergoing PCI.

The correlation between OSA and risk of cardiovascular events in the general population has been well established in longitudinal observational studies[19] and meta-analysis,[20] whereas data on patients with known cardiovascular diseases were sparse. In 1 meta-analysis that enrolled patients with ischemic heart disease, OSA was an independent predictor of recurrent cardiac events.[21] However, the definitions of ischemic heart disease and outcome measures vary across studies, therefore precluding definitive conclusions.[21] In contrast, the present meta-analysis focused on a high-risk group of patients with established CAD (mostly ACS) and receiving PCI. Our findings suggested a higher risk of composite cardiovascular
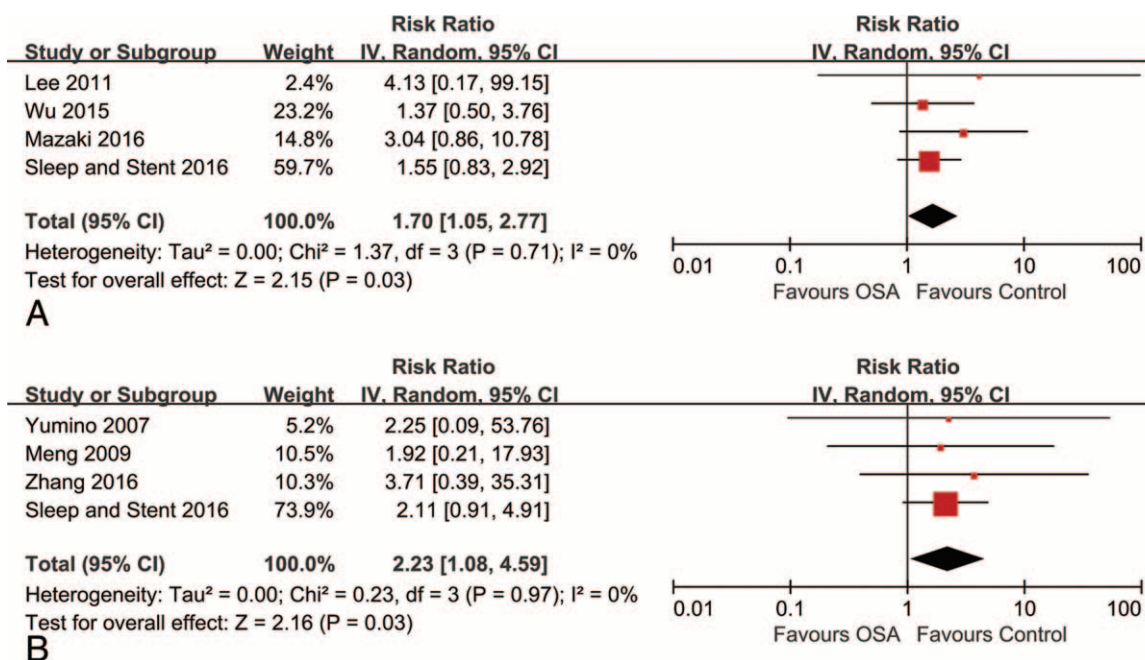
Figure 3. Risk estimates for all-cause death and cardiovascular death. Forest plot displays the risk ratio with 95% CI for all-cause death (A) and cardiovascular death (B) in patients with OSA compared to control. The diamond indicates the point estimate, and the left and right end of the line indicate the 95% CI. CI = confidence interval, IV = inverse variance, OSA = obstructive sleep apnea.
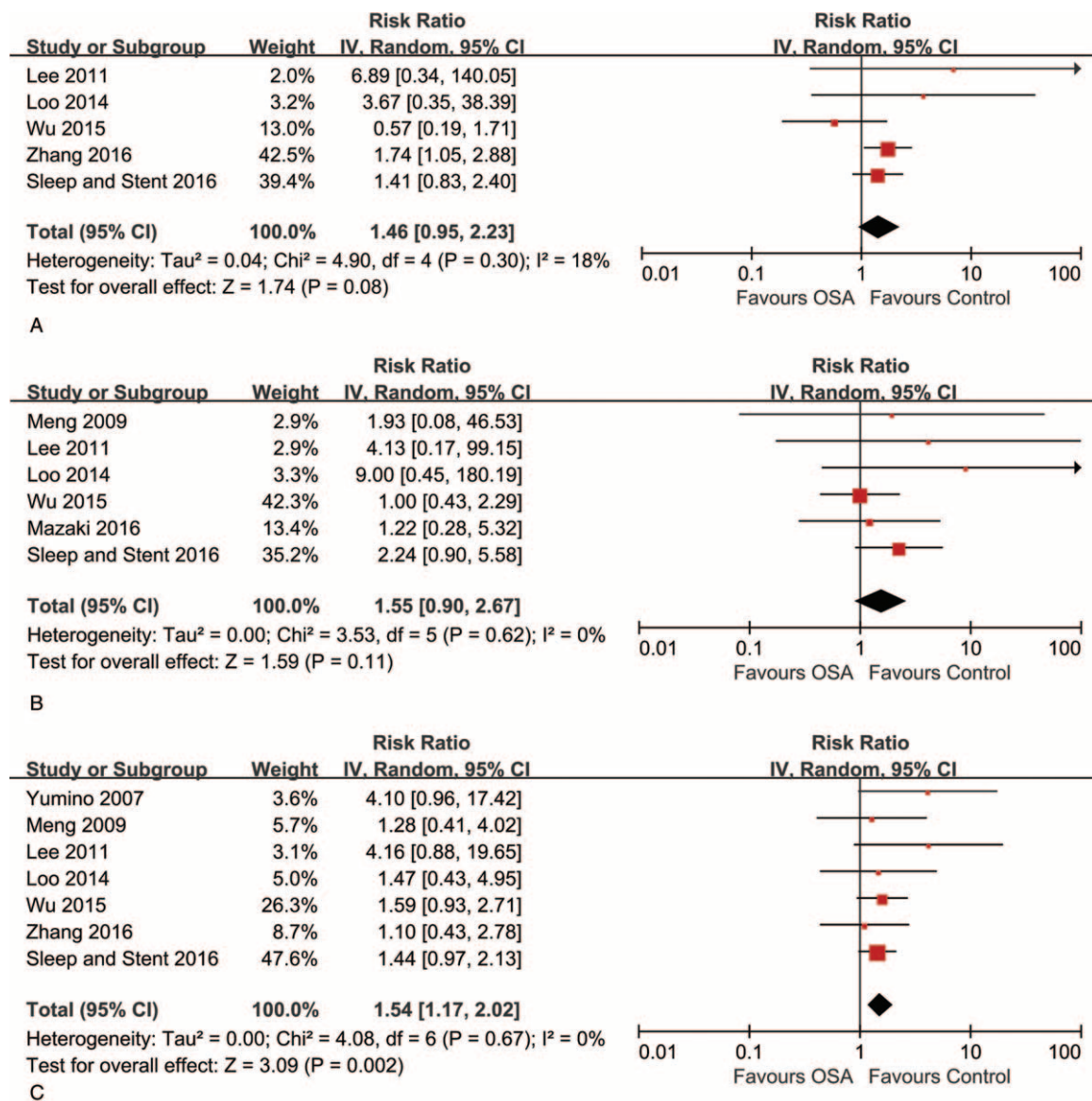
Figure 4. Risk estimates for myocardial infarction, stroke, and repeat revascularization. Forest plot displays the risk ratio with 95% CI for the outcomes of myocardial infarction (A), stroke (B), and repeat revascularization (C) in patients with OSA compared to control. The diamond indicates the point estimate, and the left and right end of the line indicate the 95% CI. CI = confidence interval, IV = inverse variance, OSA = obstructive sleep apnea.

events following PCI in patients with OSA. In the meta-analysis by Zhao et al,[22] OSA can independently increase the risk of cardiovascular events in 5 studies, which was consistent with our results. Noteworthy, we did multiple sensitivity analysis by excluding studies with retrospective cohort, unadjusted values, sample size ≤100, and follow-up duration ≤1 year, and found no change in the statistical significance or direction of effect for the primary endpoint. In terms of mortality, our results were consistent with those that reported in the general population.[20] The insignificant association for the outcomes of stroke may be due to a small number of included studies or the relatively lower risk in patients with CAD compared to those with stroke.[21]

OSA-mediated intermittent hypoxia, that is triggered by repetitive episodes of apneas and hypopneas, is being recognized as the major factor contributing to cardiovascular impairment.[23] Recurrent cycles of hypoxemia with reoxygenation promote oxidative stress, sympathetic activation, and inflammatory responses, leading to endothelial dysfunction[23] and reduction of repair capacity,[24] which are responsible for the initiation and progression of atherosclerosis. By intravascular ultrasound assessment for symptomatic CAD, patients with OSA had a larger total atheroma volume than those without OSA, even after adjustment for traditional risk factors.[4] In patients with ACS, the presence of OSA was associated with higher rate of restenosis after PCI at 6 months.[5] Our analysis showed an increased risk of repeat revascularization after PCI in patient with OSA, which further supports current evidence. OSA may also act as a trigger for nocturnal myocardial ischemia.[25] In patients presenting with MI, this could exert a continuous effect and result in less myocardial salvage and impaired cardiac function, despite after successful PCI.[26] In addition, patients with OSA showed increased platelet activation and aggregation[27] and reduced fibrinolytic capacity.[28] All these findings predispose to thrombosis or even fatal cardiovascular events, which was verified in our analysis.

Specifically, the etiology of OSA varies across patients, including general factors (male sex, age, and obesity), anatomic factors (such as small upper airway lumen), mechanical factors, poor upper airway muscle function, and low arousal threshold,[29,30] all of which would have a different impact on the subsequent cardiovascular risk. Further studies evaluating the association of specific etiology and individualized therapy with adverse events are needed.

Although OSA was found to be a significant predictor of recurrent cardiovascular events, it is prevalent that OSA is underdiagnosed by cardiologists and consequently under-treated.[31] Konecny et al[32] reviewed 798 patients who were hospitalized for acute MI and found only 12% of patients had documentation of diagnosed or suspected OSA. In contrast, more than two thirds had at least mild OSA evaluated by overnight polysomnography in a prospective cohort. In view of higher prevalence of OSA (up to 61.8% in our analysis) and subsequent cardiovascular risk, it is more reasonable and clinically significant to screen for OSA in patients with CAD and/or undergoing PCI than in the general population.

On the other hand, the low awareness of OSA may be explained by few randomized trials to assess the efficacy of continuous positive airway pressure (CPAP) as well as neutral results of current studies. In the multicenter Sleep Apnea Cardiovascular Endpoints trial that randomized 2717 participants, CPAP failed to reduce cardiovascular events in patients with moderate to severe OSA and established cardiovascular disease at a median follow-up of 3.7 years.[33] Another single-center Randomized Intervention With CPAP in Coronary Artery Disease and Sleep Apnea trial enrolled 224 patients with OSA and CAD who had undergone revascularization. The results showed no difference in a composite endpoint of repeat revascularization, MI, stroke, or cardiovascular death in patients with CPAP versus those without CPAP therapy. However, adjusted on-treatment analysis exhibited better outcomes among patients who were adherent to CPAP therapy (≥ 4 hours per night).[34] Although the beneficial effects of OSA intervention remain controversial, there is still a need for large-scale randomized trials to further explore the treatment effects of CPAP in a high-risk group with homogenous CAD populations (ACS, MI, or PCI, etc.).

4.1. Study limitations

First, we observed significant statistical heterogeneity in the risk estimate for MACE. This may be partly explained by differences in sample size, definition of outcomes, and study quality according to Newcastle-Ottava Scale score or whether adjustment for confounders was performed. Second, there is evidence of publication bias for the primary endpoint. However, the effect size remains significant after trim-and-fill analysis. Third, the stent type may have an effect on the association of OSA with cardiovascular outcomes. Therefore, we excluded patients receiving bare-metal stent or other stent types and found no change in the significance of main outcome measure. However, most included studies were conducted in the era of 1st-generation DES. The impact of OSA on recurrent events in the 2nd-generation DES era requires further evaluation. Fourth, all included studies did not report the association of different categories of OSA with cardiovascular events after PCI. The relative risk based on the severity of OSA warrants further investigation. Fifth, results of secondary individual cardiovascular events could be underpowered due to a small number of

included studies and variations in definitions of events. Sixth, this meta-analysis was not done based on patient level data. Seventh, because the included studies recruited primarily Asian patients, studies pertaining to other ethnicities are needed. Finally, the data from observational studies should be interpreted with caution. Although our analysis was predominantly based on adjusted values, the potential residual confounding remains a threat to the validity of results.

5. Conclusions

The present meta-analysis suggests that in patients undergoing PCI, the presence of OSA is associated with greater risk of recurrent MACE, all-cause death, cardiovascular death, and repeat revascularization. The results should be interpreted with caution given potential inconsistency of observational studies. Whether treatment of OSA prevents subsequent events after PCI warrants further investigation.

Author contributions

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Conceptualization: Shao-Ping Nie.
Supervision: Yong-Xiang Wei.

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