



Obstructive sleep apnea-induced multi-organ dysfunction after elective coronary artery bypass surgery in coronary heart disease patients

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Background: The aim of this study was to explore the underlying impact of obstructive sleep apnea (OSA) on postoperative parameters of multi-organ function among coronary heart disease (CHD) patients following elective coronary artery bypass grafting (CABG).

Methods: Electronic literature databases were searched manually and automatically for relevant English articles. All of the included articles focused on a comparison of the incidence of postoperative parameters of multi-organ function in CHD patients undergoing elective CABG with and without OSA. Studies were excluded if they met any one of the following criteria: (I) duplicate publication; (II) ongoing or unpublished studies; (III) only published as abstracts or conference proceedings; and (IV) less than 30 patients in the patient cohort.

Results: A total of 13 articles met our inclusion criteria. The current study demonstrated OSA significantly increased the incidence of major adverse cardiac and cerebrovascular events (MACCEs) in CHD patients undergoing elective CABG compared with the controls [odds risk (OR), 1.97; 95% CI, 1.50 to 2.59, $P < 0.0001$]. In addition, OSA was associated with an increased risk of new revascularization in CHD patients undergoing elective CABG (OR, 9.47; 95% CI, 2.69 to 33.33, $P < 0.0001$). Moreover, reintubation and tracheostomy in the OSA group was increased 243% (OR, 3.43; 95% CI, 1.35 to 8.71; $P = 0.009$) and 372% (OR, 4.72; 95% CI, 1.23 to 18.13; $P = 0.024$), respectively, compared with the control group. Besides, we also confirmed OSA significantly increased the acute kidney injury (AKI) incidence by 124% (OR, 2.24; 95% CI, 1.07 to 4.72; $P < 0.0001$).

Conclusions: OSA may contribute to postoperative multi-organ dysfunction among CHD patients undergoing elective CABG by increasing the incidence of MACCEs, especially new revascularization, as well as respiratory, and renal complications.

Keywords: Obstructive sleep apnea (OSA); coronary heart disease (CHD); elective coronary artery bypass grafting (CABG); postoperative multi-organ dysfunction

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Introduction

Obstructive sleep apnea (OSA), a syndrome caused by repeated narrowing of the throat during sleep, is a common breathing-associated sleep disorder with recent estimates of prevalence in the general adult population ranging from 9% to 38% (1,2). In coronary heart disease (CHD) patients undergoing elective coronary artery bypass grafting (CABG), the incidence of mild OSA [$5 \leq$ apnea-hypopnea index (AHI) <15] and moderate to severe OSA (AHI ≥ 15) is 74% and 48%, respectively (3). Despite the high prevalence of OSA among CHD patients following CABG, the impact of OSA in the postoperative multi-organ function is not well established. Most of the evidence is focused on arrhythmia recurrence after cardiac surgery (4,5), the effects of OSA on respiratory as well as renal parameters still need to be investigated further. In addition, as for the cardio-cerebrovascular complications, recent studies are based on patients diagnosed with different cardiac diseases undergoing various types of elective cardiac surgeries (6-8). Data on CHD patients developing postoperative complications after CABG are sparse. So far, no meta-analyses have focused on documenting a direct correlation between CHD patients following elective CABG with OSA and a higher risk of adverse cardiac and cerebral vascular events.

This current meta-analysis was initiated to fill the above knowledge gaps. We particularly focused on CHD patients with or without OSA. The aim of this study was to explore the underlying impact of OSA on postoperative parameters of multi-organ function, including cardiac and cerebral vascular, respiratory as well as renal postoperative complications, among CHD patients following elective CABG. Recognition of the association and determinants of OSA on postoperative multiple organ dysfunction should lead to strategies to improve the prognosis of CHD patients undergoing elective CABG.

Methods

Literature search and selection criteria

This systematic review and meta-analysis were conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (9) (available at <http://dx.doi.org/10.21037/jtd-20-2037>). Electronic literature databases, including PubMed, ISI Web of Science, Directory of Open Access Journals, and the Cochrane Library electronic databases, were searched manually and automatically for

relevant English articles. All of the selected articles focused on a comparison of the incidence of primary and secondary outcomes in CHD patients undergoing elective CABG with and without OSA.

As for further full-text assessment. The references of the retrieved articles were also reviewed to identify additional eligible studies. The study selection program was shown in *Figure 1*. Studies meeting the following criteria were included:

The following search terms were used: (“sleep apnea” [All Fields] OR “sleep apnea” [All Fields]) AND (“CABG” [All Fields] OR “coronary artery bypass grafting” [All Fields]) AND (“major adverse cardiac and cerebrovascular events” [All Fields] OR “cardiovascular outcomes” [All Fields] OR “major cardiovascular and cerebrovascular adverse events” [All Fields]).

The last search was conducted on July 1, 2019. Two investigators (J.W. and W.Y.) performed the initial search separately, deleted duplicate records, screened titles and abstracts for relevance, and identified relevant article:

- (I) Patients: subjects were CHD patients following elective CABG.
- (II) Intervention: elective CABG.
- (III) Comparison: CHD patients undergoing elective CABG with preoperative OSA vs. CHD patients undergoing elective CABG without preoperative OSA.
- (IV) Outcomes: multi-organ parameters, including cardiac, respiratory and renal parameters; in-hospital death; infection; intensive care unit (ICU)-readmission; length of ICU stay; length of hospital stay.
- (V) Study design: observational studies (prospective or retrospective cohort studies) were included in this meta-analysis.

Studies were excluded if they met any one of the following criteria: (I) duplicate publication; (II) ongoing or unpublished studies; (III) only published as abstracts or conference proceedings; and (IV) less than 30 patients in the patient cohort.

Data extraction and quality assessment

Two reviewers (J.W. and W.Y.) independently extracted the following information from the eligible studies: first author, year of publication, country, study design, patient characteristics, number of patients enrolled, intervention, and outcome data. When the same patients were reported in several publications, only the largest study was retained to avoid duplication of information. The current study used the Downs and Black score system to evaluate the quality

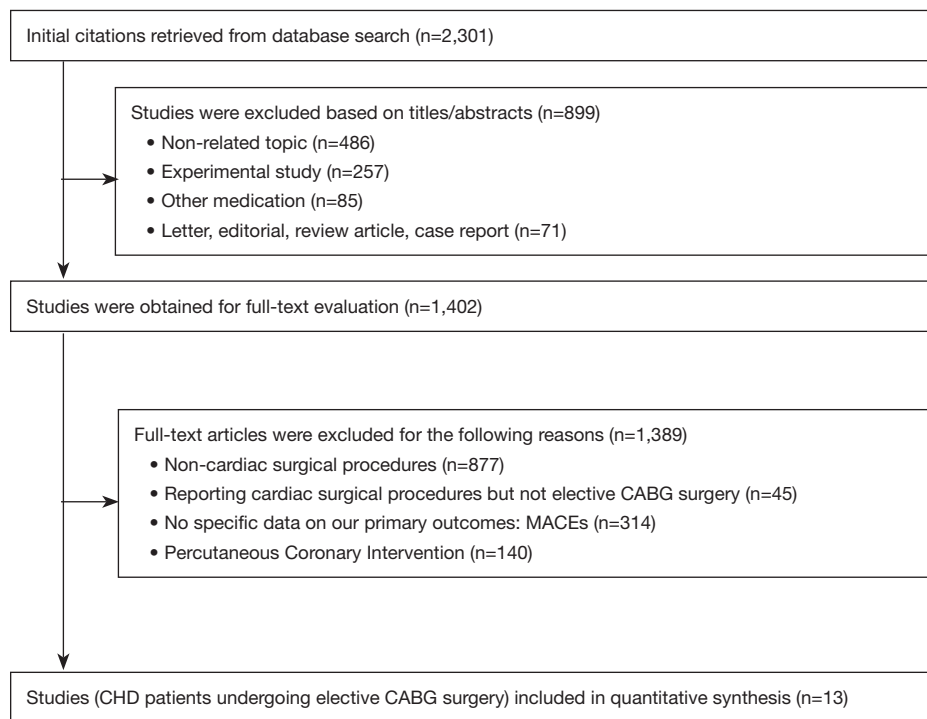


Figure 1 Flow diagram of study selection.

of each study. The quality of studies with a score ≥ 20 was considered good and a score < 20 was considered poor.

Study end points and OSA definition

The AHI was defined as the average number of episodes of apneas and hypopneas per hour of sleep. OSA must be diagnosed by polysomnography (PSG), which was defined in events per hour as $AHI \geq 5$ or screened as “high-risk OSA” by screening questionnaires.

Diagnosis of OSA and pre-/postoperative continuous positive airway pressure (CPAP) use in patients with OSA were shown in *Table 1*. Endpoints were as follows: (I) A composite end point of major adverse cardiac and cerebrovascular events (MACCEs) up to 30 days after surgery, including: cardiac death, myocardial infarction (MI), myocardial injury, nonfatal cardiac arrest, new revascularization (PCI or CABG), deep venous thrombosis, newly documented postoperative atrial fibrillation (POAF), postoperative cerebral vascular accident (CVA) or transient ischemic attack (TIA), and congestive heart failure. MACCEs and variables of major morbidity defined as in the Society of Thoracic Surgeons (STS) national database (10). (II) Respiratory complications were respiratory failure or major pulmonary complications. Postoperative respiratory failure was

defined as the need for prolonged mechanical ventilation of > 24 h or the development of airway complications, including the need of reintubation or tracheostomy. Acute respiratory distress syndrome (ARDS), pneumonia, or pulmonary embolism represented major pulmonary complications. Renal complications included postoperative acute kidney injury (AKI) according to the KDIGO (Kidney Disease: Improving global outcomes) criteria.

Statistical analysis

Differences are expressed as odds risk (OR) or standardized mean difference (SMD) with 95% CI. Study heterogeneity was tested using the I^2 statistic. Heterogeneity was considered to be low in studies with an I^2 between 25% and 50%, moderate in studies with an I^2 between 50% and 75%, and high in studies with an I^2 exceeding 75%. I^2 exceeding 50% represents significant heterogeneity. A fixed-effects model was used when study heterogeneity was not significant; a random-effects model was used when study heterogeneity was significant. Funnel plots and the Egger linear regression test were used to estimate publication bias. Meta-regression analysis was performed to examine whether the pooled outcomes could be modified by the confounding factor. A Q

Table 1 Diagnosis of OSA and pre-/postoperative CPAP use in patients with OSA

Reference	Screening and/or diagnostic tool	Patients on preoperative CPAP use (n)	Patients on postoperative CPAP	when was screened for OSA
Moore <i>et al.</i>	PSG	None	None	Before surgery
Kaw <i>et al.</i>	PSG	None	None	Before surgery
Bhama <i>et al.</i>	PSG	None	None	Before surgery
Sharma <i>et al.</i>	Questionnaire	None	None	Before surgery
Mungan <i>et al.</i>	Questionnaire	NR	NR	Before surgery
Amra <i>et al.</i>	Questionnaire	NR	NR	Before surgery
Oosten <i>et al.</i>	PSG	63%	None	Before surgery
Wong <i>et al.</i>	PSG	44%	None	Before surgery
Foldvary-Schaefer <i>et al.</i>	PSG	None	None	Before surgery
Zhao <i>et al.</i>	PSG	None	NR	Before surgery
Uchôa <i>et al.</i>	PSG	None	None	Before surgery
Patel <i>et al.</i>	Questionnaires	100%	100%	Before surgery
Tafelmeier <i>et al.</i>	PSG	NR	NR	Before surgery

OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; NR, not report; PSG, polysomnography.

model statistic was used in the meta-regression. All P values are two-sided. Statistical analyses were conducted by using Stata 15.0 software (StataCorp LP, College Station, TX).

Results

Study selection, characteristics and quality assessment

The selection process is illustrated in *Figure 1*. A total of 13 articles met our inclusion criteria (3,11-22). The main characteristics of the included studies are described in *Table 2*. Total primary and secondary pooled outcomes in patients with and without OSA were demonstrated in *Table 3*. Of the 13 reports, three contained CHD patients following elective CABG + valvular surgery (3,12,19). Meta-regression analysis was performed to examine whether the above pooled outcomes could be modified by the valvular surgery. The results were shown in *Table 3*. In addition, Downs and Black Score analysis revealed that all of the 13 articles had good quality (score ≥ 20 , *Table 2*).

The impact of OSA on postoperative cardiac and cerebrovascular parameters in CHD patients following elective CABG (primary outcomes, Figure 2, Table 3)

The current study demonstrated OSA significantly

increased the incidence of MACCEs in CHD patients undergoing elective CABG compared with the controls (OR, 1.97; 95% CI, 1.50 to 2.59, $P < 0.0001$; *Figure 2A* and *Table 3*) without significant heterogeneity ($I^2 = 9.3\%$) and publication bias ($P = 876$). The funnel plot also showed low publication bias (*Figure 3*). No significant effects were detected in meta-regression analysis with respect to the examined covariate ($P = 0.665$, *Table 3*); namely, the valvular surgery. In addition, OSA was associated with an increased risk of new revascularization, including CABG and percutaneous coronary intervention (PCI), in CHD patients undergoing elective CABG (OR, 9.47; 95% CI, 2.69 to 33.33, $P < 0.0001$; *Figure 2D* and *Table 3*) without significant heterogeneity ($I^2 = 0.0\%$). Since all the included patients in this endpoint underwent CABG alone, the confounding factor had no effects on the pooled outcome. Furthermore, the current meta-analysis confirmed OSA did not affect the incidence of postoperative MI and CVA or TIA (*Figure 2B,C* and *Table 3*).

The impact of OSA on postoperative respiratory and renal parameters in CHD patients following elective CABG (secondary outcomes, Figures 4,5, Table 3)

The current study demonstrated that reintubation in the

Table 2 Patient characteristics and down and black scores

Reference	Setting	Selective CABG surgery	CABG-OSA/control			Reported organ outcomes	Downs and black score	The severity of OSA
			Patients, No.	Mean age, y	Male, %			
Moore <i>et al.</i>	OB, single center (Sweden)	CABG alone	78/39	62/61.3	NR	Cardiac	22	Mild, moderate and severe OSA
Kaw <i>et al.</i>	OB single center (United States)	CABG ± valve	29/146	62/61	78/77	Cardiac, Renal, Pulmonary	21	Mild, moderate and severe OSA
Bhama <i>et al.</i>	OB single center (United States)	CABG alone	20/65	65/65	100/100	Cardiac, Pulmonary	20	Mild, moderate and severe OSA
Sharma <i>et al.</i>	OB single center (United States)	CABG alone	81/40	60/59	69/31	Cardiac, Pulmonary	21	Mild, moderate and severe OSA
Mungan <i>et al.</i>	OB, single center (Turkey)	CABG alone	33/40	NR	NR	Cardiac	20	Mild, moderate and severe OSA
Amra <i>et al.</i>	OB, single center (Iran)	CABG alone	25/36	61.1/57.3	72/83	Cardiac, Pulmonary	23	Mild, moderate and severe OSA
Oosten <i>et al.</i>	OB, single center (Canada)	CABG alone	132/145	63/66	80/76	Cardiac, Pulmonary	24	Mild, moderate and severe OSA
Wong <i>et al.</i>	OB, single center (United States)	CABG alone	26/195	67/65	79/66	Cardiac, Renal, Pulmonary	22	Mild, moderate and severe OSA
Foldvary-Schaefer <i>et al.</i>	OB, single center (United States)	CABG ± valve	45/28	NR	NR	Cardiac, Pulmonary	21	Moderate and severe OSA
Zhao <i>et al.</i>	OB, single center (Singapore)	CABG alone	128/32	61/63	86/81	Cardiac, Renal	21	Mild, moderate and severe OSA
Uchôa <i>et al.</i>	OB, single center (Brazil)	CABG alone	37/30	59/55	84/63	Cardiac, Pulmonary	25	Moderate and severe OSA
Patel <i>et al.</i>	OB, single center (United States)	CABG ± valve	31/178	NR	67.7/74.1	Cardiac, Pulmonary	22	Mild, moderate and severe OSA
Tafelmeier <i>et al.</i>	OB, single center (Germany)	CABG alone	23/77	72/67	91/82	Cardiac, Renal, Pulmonary	23	Moderate and severe OSA

CABG, Coronary Artery Bypass Grafting; OSA, obstructive sleep apnea; OB, observational study

OSA group was increased by 243% compared with the control group (OR, 3.43; 95% CI, 1.35 to 8.71; $P=0.009$; *Figure 4B, Table 3*) but with significant heterogeneity ($I^2=50.0\%$). Meanwhile, patients with OSA group showed a 372% increase in tracheostomy compared with the control group (OR, 4.72; 95% CI, 1.23 to 18.13; $P=0.024$; *Figure 4C, Table 3*) without significant study heterogeneity ($I^2=0.0\%$). Furthermore, we found OSA did not affect the incidence of postoperative major pulmonary complications and pulmonary edema (*Figure 4A,D and Table 3*). In meta-regression analysis, we found the examined covariate, namely, the valvular surgery, had no significant effect on the above pooled outcomes.

We also confirmed OSA significantly increased the

AKI incidence by 124% (OR, 2.24; 95% CI, 1.07 to 4.72; $P<0.0001$; *Figure 5 and Table 3*) without significant study heterogeneity ($I^2=0.0\%$). In meta-regression analysis, we found the examined covariate, namely, the valvular surgery, had no significant effect on the above pooled outcomes.

The impact of OSA on postoperative exploratory parameters in CHD patients undergoing elective CABG (exploratory outcome, Table 3)

Our results demonstrated that OSA increased medical resource utilization including length of postoperative hospital stay (SMD, 0.30; 95% CI, 0.12 to 0.47; $P<0.0001$; *Table 3*) and ICU stay (SMD, 0.30; 95% CI, 0.16 to 0.44;

Table 3 Total primary and secondary pooled outcomes in patients with and without OSA and meta-regression examining whether the above pooled outcomes could be modified by the confounding factor

Outcomes	Sample size		NO. of included references	Heterogeneity, I ² (%)	Pooled OR/SMD	95% CI	P value	Selective CABG surgery	Confounding factor: CABG ± valve
	CABG-OSA	No CABG-OSA							
Primary outcomes									
Postoperative cardiac and cerebrovascular parameters									
MACCEs, n (%) [*]	209/688	145/1,051	13	9.3	1.97	1.50–2.59	<0.0001	CABG ± valve	0.20 (–0.69, 1.09)/0.665
Post-MI, n (%)	10/105	22/135	3	0.0	1.30	0.53–3.17	0.571	CABG ± valve	–0.84 (–3.80, 2.13)/0.581
Post-TIA or CVA, n (%)	8/236	5/285	4	0.0	2.24	0.64–7.89	0.653	CABG ± valve	–1.02 (–3.57, 1.51)/0.427
New revascularization, PCI/CABG, n (%) [*]	15/60	4/107	2	0.0	9.47	2.69–33.33	<0.0001	CABG alone	None
Secondary outcomes									
Postoperative respiratory parameters									
Major pulmonary complications, n (%)	22/134	32/281	4	0.0	1.19	0.62–2.30	0.603	CABG ± valve	–0.84 (–0.22, 0.51)/0.224
Reintubation, n (%) [*]	40/383	27/765	8	50.0	3.43	1.35–9.71	0.009	CABG ± valve	–1.51 (–3.03, 0.01)/0.051
Tracheostomy, n (%) [*]	7/94	4/300	3	0.0	4.72	1.23–18.13	0.024	CABG ± valve	–1.39 (–4.14, 1.46)/0.349
Pulmonary edema, n (%)	22/60	66/107	2	0.0	1.48	0.43–5.08	0.536	CABG alone	None
Postoperative renal parameters									
AKI, n (%) [*]	18/205	35/450	4	0.0	2.24	1.07–4.72	0.033	CABG ± valve	–0.72 (–3.08, 1.64)/0.551
Exploratory parameters									
In-hospital death, n (%)	9/316	13/675	7	0.0	1.62	0.64–4.07	0.307	CABG ± valve	–0.63 (–2.53, 1.28)/0.518
Infection, n (%)	16/203	14/315	5	0.0	1.24	0.57–2.71	0.591	CABG ± valve	0.29 (–1.83, 2.41)/0.788
ICU-readmission	2/25	3/36	3	0.0	1.68	0.67–4.20	0.264	CABG ± valve	0.37 (–1.49, 2.23)/0.696
Length of ICU stay	NE	NE	6	30.6	0.30 (SMD)	0.12–0.47	<0.0001	CABG ± valve	–0.02 (–1.84, 1.80)/0.982
Length of hospital stay	NE	NE	7	20.8	0.30 (SMD)	0.16–0.44	<0.0001	CABG ± valve	1.25 (–1.67, 4.17)/0.402

^{*}, P<0.005. CABG, coronary artery bypass grafting; OSA, obstructive sleep apnea; SE, standard error; OR, odds ratio; SMD, standardized mean difference; CI, confidence interval; MACCEs, major adverse cardiovascular and cerebral events; MI, myocardial infarction; TIA, transient ischemic attack; CVA, cerebral vascular accident; PCI, percutaneous coronary intervention; AKI, acute kidney injury.

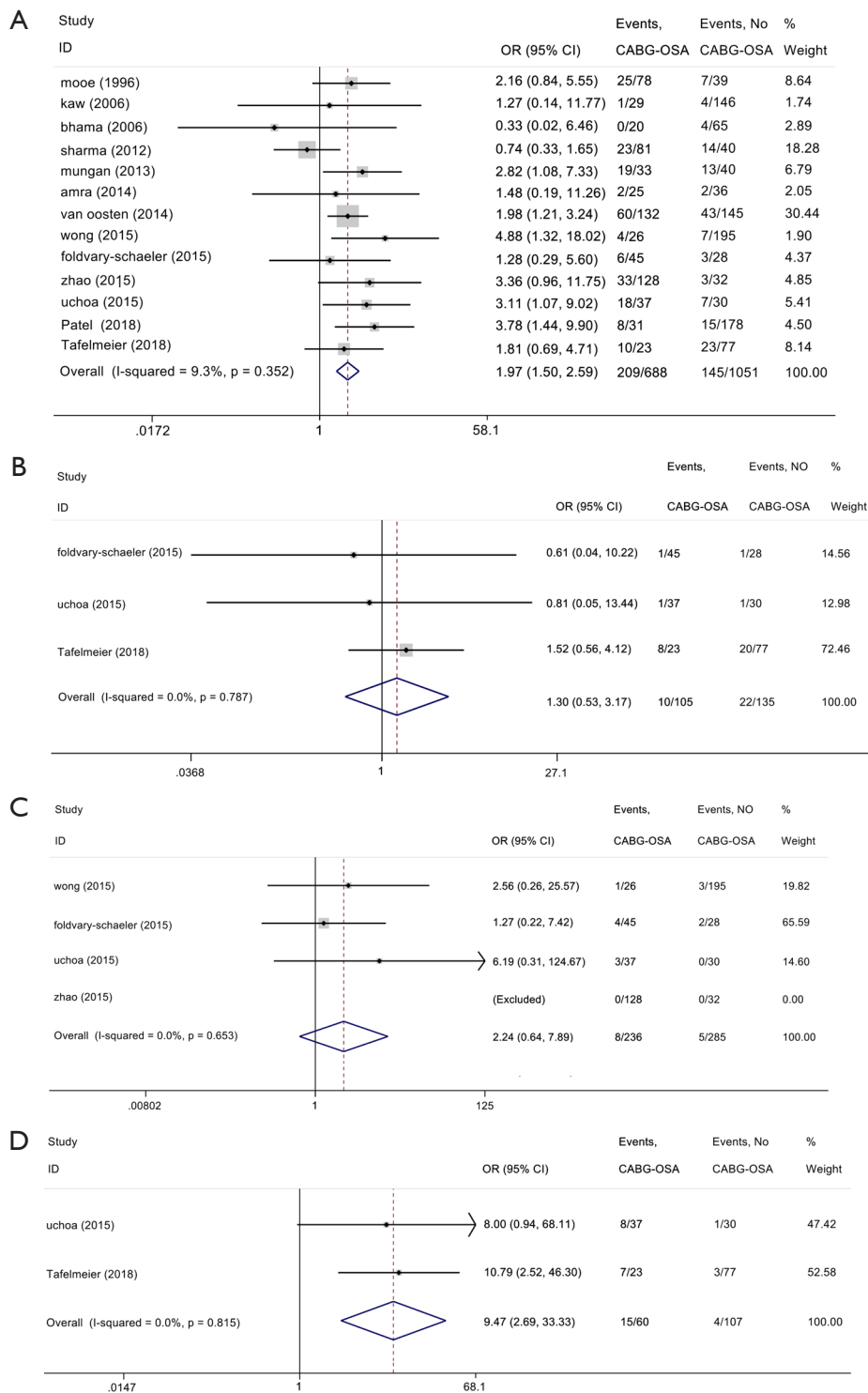


Figure 2 The impact of OSA on postoperative cardiac and cerebrovascular parameters in CHD patients following elective CABG. Cardiac and cerebrovascular parameters: (A) MACCEs; (B) MI; (C) CVA or TIA; (D) New revascularization, including CABG and PCI. OSA, obstructive sleep apnea; CHD, coronary heart disease; CABG, coronary artery bypass grafting; MACCEs, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; CVA, cerebral vascular accident; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; OR, odds risk; CI, confidence interval.

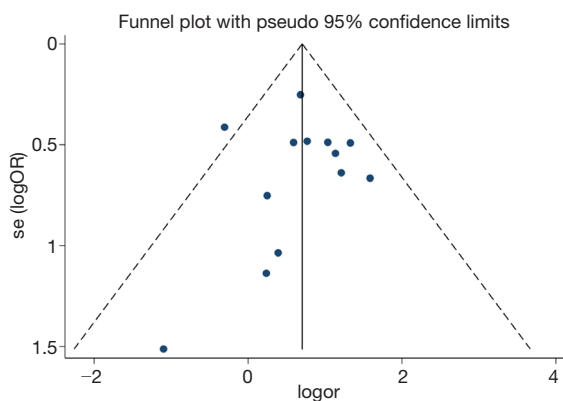


Figure 3 The funnel plot shows low publication bias.

$P < 0.0001$; *Table 3*) without significant study heterogeneity. On the contrary, OSA did not affect the incidence of postoperative in-hospital death, infection and ICU-readmission (*Table 3*). In meta-regression analysis, we found the examined covariate, namely, the valvular surgery, had no significant effect on the above pooled outcomes.

Meta-regression Analysis of the Potential Modifiers

Meta-regression analysis demonstrated the above pooled outcomes could not be modified by the valvular surgery (*Table 3*). Furthermore, the results also shown the above pooled outcomes were not affected by the following modifiers, including confirmation of OSA (PSG or not); quality of study; loss of patients due to follow-up and OSA with CPAP treatment (*Table 4*).

Discussion

To the best of our knowledge, this is the first meta-analysis to comprehensively examine the association between OSA and postoperative multi-organ dysfunction in CHD patients undergoing elective CABG. Our key findings are: (I) compared with the control group, OSA significantly increased the incidence of MACCEs in CHD patients undergoing elective CABG. In addition, OSA was associated with an increased risk of new revascularization, including CABG and PCI, in CHD patients undergoing elective CABG; (II) reintubation in the OSA group was increased compared with the control group. Meanwhile, patients with OSA group showed an increase in tracheostomy compared with the control group; (III) OSA significantly increased the AKI incidence compared with the control group; (IV) we

also confirmed the association between OSA and increased medical resource utilization.

In the past 10 years, only one meta-analysis had investigated the effects of preoperative OSA on postoperative MACCEs among patients following cardiac surgery (6). However, the heterogeneity of the results cannot be ignored ($I^2=64\%$). Previous meta-analysis focused on patients with varying cardiovascular diseases, including CHD, valvular heart disease and aortic disease, which might account for the source of the huge heterogeneity and led to inaccurate pooled results. In this current meta-analysis, we reduced the heterogeneity by including only CHD patients alone. For CHD patients undergoing CABG + the valvular surgery, meta-regression showed no significant effect on our pooled outcomes. In addition, there is another limitation in the previous meta-analysis. Insufficiency of the pooled postoperative endpoints other than MACCEs had impeded meaningful conclusions in cardiac surgical patients. The current research systematically examined the association between OSA and postoperative multi-organ dysfunction, including the parameters of cardiac and cerebral vascular, respiratory and renal function, in CHD patients undergoing elective CABG. The findings of this study might shed new light on optimizing the preoperative risk assessment for postoperative multi-organ dysfunction as well as the peri- and postoperative management of CHD patients undergoing elective CABG.

Previous studies investigating the effects of OSA on postoperative cardiac events among CHD patients following CABG show controversial results. For instance, Ucho^a and colleagues (14) did not find a significant increase in MACCEs (including POAF) among CHD patients undergoing CABG with OSA in the short-term follow-up. On the contrary, Tafelmeier and colleagues (13) demonstrated sleep-disordered breathing, particularly OSA, is associated with adverse cardiac events after CABG, independent of known confounders. The findings of our study are in accordance with previous studies that found OSA significantly increased the incidence of MACCEs in CHD patients undergoing elective CABG. Notably, the current meta-analysis firstly confirmed OSA was associated with an increased risk of new revascularization. The discovery may have far more profound implications for peri- and postoperative management of CABG. Since previous studies showed that new or repeated revascularization in patients with triple-vessel disease independently increased the risk for ICU-associated adverse outcomes and postoperative hospital and ICU

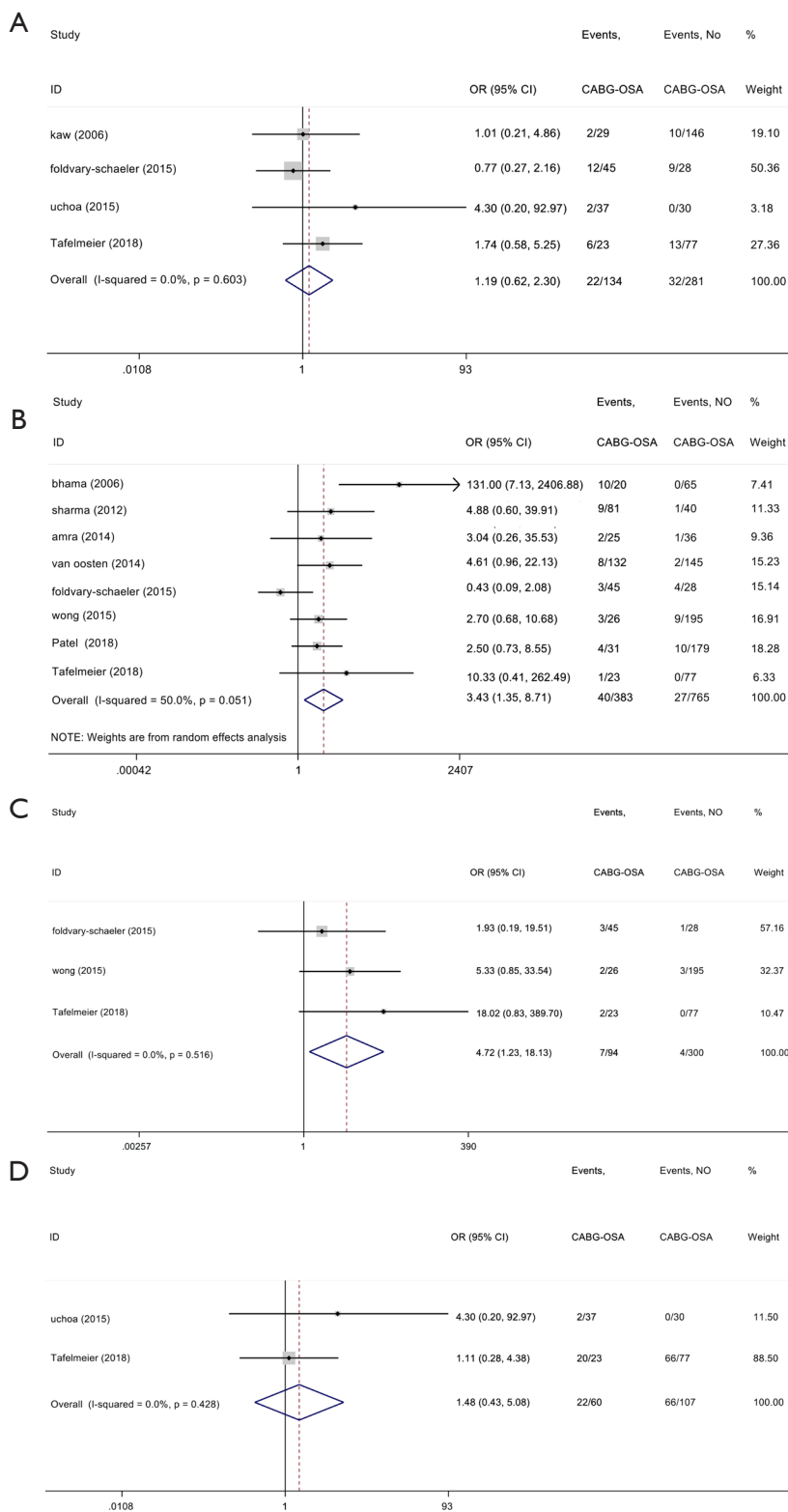


Figure 4 The impact of OSA on postoperative respiratory or airway parameters in CHD patients following elective CABG. Respiratory parameters: (A) Postoperative major pulmonary complications; (B) reintubation; (C) tracheostomy; (D) pulmonary edema. OSA, obstructive sleep apnea; CHD, coronary heart disease; CABG, coronary artery bypass grafting; OR, odds risk; CI, confidence interval.

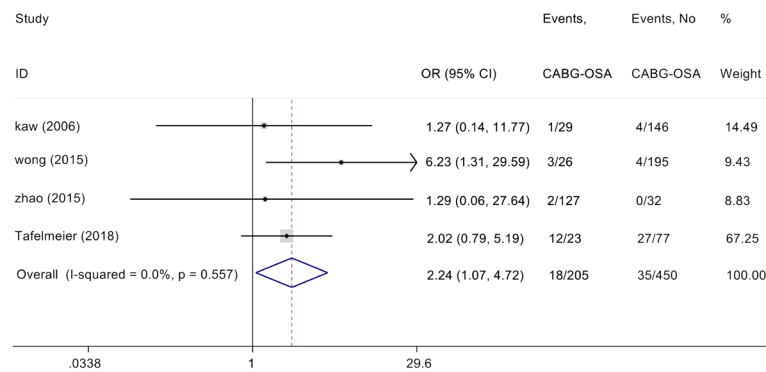


Figure 5 The impact of OSA on postoperative AKI in CHD patients following elective CABG. OSA, obstructive sleep apnea; CHD, coronary heart disease; CABG, coronary artery bypass grafting; AKI, Acute kidney injury; OR, odds risk; CI, confidence interval.

Table 4 Meta-regression for OSA and postoperative composite outcomes

Meta-regression variables	MACCEs		Major pulmonary complications		Reintubation		AKI	
	Exp (b)	P value	Exp (b)	P value	Exp(b)	P value	Exp(b)	P value
Confirmation of OSA (PSG or not)	0.876	0.359	0.375	0.578	0.724	0.772	0.818	0.904
Quality of study	0.517	0.479	1.047	0.126	1.004	0.379	0.725	0.884
Loss of patients due to follow-up	0.997	0.871	NE	NE	1.475	0.127	NE	NE
OSA with CPAP treatment	0.224	0.529	1.035	0.810	0.780	0.325	1.156	0.587

AKI, acute kidney injury; MACCEs, major adverse cardiac and cerebrovascular events; Exp(b) is the value of the risk ratio of continuous variables; PSG, Polysomnography; NE, not enough studies; CPAP, continuous positive airway pressure.

stay (23-25), the current study further demonstrated OSA may contribute to the development of above parameters by causing new or repeated revascularization. The mechanisms underlying OSA-associated adverse cardiac events among CHD patients undergoing CABG may be correlated to the following aspects: endothelial function, arterial stiffening, as well as systemic inflammation. Our previous meta-analysis of 18 studies aimed to investigate the mechanisms underlying OSA-associated cardiovascular events (1). We demonstrated OSA, particularly moderate-severe OSA, was significantly associated with impaired endothelial function (measured by flow mediated dilation and nitroglycerin-induced dilation), increased arterial stiffness (determined by carotid-femoral pulse wave velocity and indicates augmentation index), and elevated serum levels of inflammatory markers (such as high-sensitivity C-reactive protein and C-reactive protein), independent of known confounders (1). The above factors were often

used to predict cardiovascular events in general and morbid populations, especially in CHD patients undergoing CABG (26-28). Besides, postoperative troponin T levels, correlated with end-organ damages, suggesting the primary role of an ischemic trigger of end-organ damages (26). Although the recent study demonstrated no differences in the myocardial infarction occurrence in CHD patients undergoing CABG with and without OSA, previous studies indicated the potential role of OSA-associated myocardial ischemia in triggering adverse cardiac events (including POAF) among cardiac surgical patients (14,29). High-quality randomized controlled trials are still needed to confirm. Finally, limited by the original literature, the current meta-analysis confirmed OSA did not affect the incidence of postoperative CVA or TIA. However, in an observational study of 392 men and women with CHD referred for coronary angiography, Valham *et al.* demonstrated OSA is an independent predictor for stroke among CHD patients (30).

Possible factors accounting for OSA-associated stroke among CHD patients include apnea-induced nocturnal cerebral ischemia, hypertension, as well as an increased risk of arteriosclerosis (31-33), which are further correlated to stroke. It is worth mentioning that, the independence relationship between sleep-disordered breathing and postoperative heart failure has been confirmed, which contributes to the increased risk of MACCEs (13). Last but not least, previous study demonstrated the rate of D-dimer positivity was higher among cases diagnosed with severe OSA compared to the rest of study population (17.6%) and indicated that severe-OSA can be a significant risk factor for deep venous thrombosis (34). However, we were limited by the small number of eligible studies and were unable to further examine the correlation between OSA and deep venous thrombosis among CHD patients undergoing CABG. Randomized controlled trials are still needed.

The current study demonstrated there is close relationship between OSA and airway complications, leading to the development of respiratory failure. Reintubation and tracheostomy in the OSA group was increased by 243% and 372%, respectively, compared with the control group. Both delayed and premature extubation may be correlated to an increased risk of various complications (35,36), and the need for reintubation or tracheostomy was viewed as a potential adverse event after CABG (35-37). Previous studies found that requiring reintubation or tracheostomy was associated with organ dysfunction, especially respiratory failure, secondary to physiologic stress, increased mortality, higher hospital costs and longer length of ICU stay (38-40). Among CHD patients following CABG, OSA was correlated to a longer intubation time (3,21). Guidelines and statements concerning postoperative care in OSA patients undergoing surgery recommend OSA is a relative risk factor for difficult mask ventilation. Plans for difficult airway management should be considered and implemented (41). The current research further confirmed that OSA may contribute to adverse events by increasing the incidence of postoperative reintubation and tracheostomy in CHD patients undergoing CABG. As for major pulmonary complications, previous studies found the patients with OSA undergoing surgery were at a greater risk for increased pulmonary edema, which could further affect the outcomes of the surgery (41-43). However, the impact of OSA on the incidence of major pulmonary complications among CHD patients undergoing CABG still need to be further confirmed by randomized controlled trials.

Currently, no evidence-based studies investigating the

effects of OSA on postoperative renal function among CHD patients following CABG. Available reports on the association between OSA and the incidence of AKI after cardiac surgery show conflicting results. In an observational study, Wong *et al.* found that OSA increased the incidence of postoperative AKI and required renal replacement therapy during hospitalization (16). In contrast, Kaw *et al.* found that OSA exerted no adverse effects on renal function after cardiac surgery (19). We firstly confirmed OSA significantly increased the AKI incidence (by 124%) compared with the control group. The mechanism underlying the adverse effects of OSA on renal outcomes among cardiac surgical populations still need to be investigated further. An animal model of sleep apnea demonstrated fibrotic changes and inflammatory in the kidney that were attributed to the impacts of intermittent hypoxia (44). In addition, previous study also reported nocturnal hypoxemia in OSA patients is correlated to accelerated renal dysfunction, possibly because of increased activity of the renal renin-angiotensin system (RAS) as well as glomerular hypertension (45). Moreover, CHD patients following CABG with OSA are also at increased risk of developing preoperative hypertension and diabetes, both of which are closely associated with AKI (46). Moreover, in an observational study, Tafelmeier *et al.* assessed the incidence of AKI after elective CABG in CHD patients without sleep-disordered breathing (SDB), with central sleep apnea (CSA), or with OSA. They demonstrated OSA was correlated to impaired renal function as observed by significantly higher creatinine values and significantly lower glomerular filtration rates than those of patients in the other two groups (13).

Our results demonstrated that OSA increased medical resource utilization including length of postoperative hospital stay and ICU stay. An increased length of stay (LOS) in ICU for OSA group suggests that CHD patients with OSA may require greater ventilatory support and longer monitoring after CABG, because of OSA-induced postoperative multi-organ dysfunction. Based on this knowledge, peri- and postoperative management of CHD patients with OSA may be optimized to minimize the rate of postoperative cardio-cerebrovascular, respiratory, as well as renal complications, further reducing the consumption of limited medical resources.

Since OSA may contribute to postoperative multi-organ dysfunction among CHD patients undergoing elective CABG, routine sleep apnea screening before CABG need to be conducted for a diagnosis to be firmly established and to determine the type and severity of OSA that will

dictate treatment alternatives. PSG is the gold standard for confirming the presence of OSA (3). However, PSG is costly and time-consuming (26). This justified the development of ambulatory abbreviated cardiorespiratory recording techniques and establishment of guidelines for the use of these devices (27). In addition, serious complications after CABG have attracted extensive attention increasingly. Previous review study found the rate of CABG-associated in-hospital morbidity and mortality is up to 14.0% and 2.0%, respectively (47). As for OSA-associated complications, since the current meta-analysis demonstrated that OSA significantly increased the incidence of MACCEs, reintubation, tracheostomy and AKI by 97%, 243%, 372%, and 124%, respectively, among CHD patients undergoing CABG, preventive measurements on OSA in the perioperative phase are needed so as to ultimately improve CHD patient in-hospital outcomes from CABG. It has been confirmed in many relevant literatures perioperative CPAP use in CHD patients with OSA was associated with a decreased rate of cardiac complications after cardiac surgery (6,14,16). Perioperative CPAP use is recommended and may optimize the condition of surgical patients with OSA (6). However, whether perioperative CPAP use would be specifically beneficial to reverse the association of CABG-OSA-related respiratory and renal dysfunction, it still needs to be confirmed.

Conclusions

There are some limitations to the findings of this current research since the absence of randomized controlled trials. Selection bias and treatment bias, inherent to the observational studies, may exist. Moreover, in the current study, heterogeneity was reduced by including only CHD patients alone. Limited by the original literature, we also included CHD patients undergoing CABG + the valvular surgery. Although meta-regression showed the valvular surgery did not affect on our pooled outcomes, high-quality randomized controlled trials focusing on CHD patients undergoing isolated CABG are still needed in the future. In addition, since the sample size of each original studies limitations, currently we cannot further address the effects of mild, moderate as well as severe OSA on multiple organ dysfunction, respectively, in CHD patients undergoing CABG.

In conclusion, the current evidence-based research demonstrated OSA may contribute to postoperative multi-organ dysfunction among CHD patients undergoing elective CABG by increasing the incidence of MACCEs,

especially new revascularization (including CABG and PCI), as well as respiratory, and renal complications. Furthermore, our results also demonstrated that OSA increased medical resource utilization including length of postoperative hospital stay and ICU stay. Based on this knowledge, peri- and postoperative management of CHD patients with OSA may be optimized to minimize the rate of postoperative parameters of multi-organ dysfunction, further reducing the consumption of limited medical resources.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was reviewed and approved by the ethics committee of all participant institutes in the Beijing An Zhen Hospital Capital Medical University.

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