

## Review Article

# Sleep apnea is a risk factor of postoperative complications after joint arthroplasty or revision joint arthroplasty: a systematic review and meta-analysis

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**Abstract:** Objective: To investigate the relationship between sleep apnea (SA) and postoperative complications after joint arthroplasty or revision joint arthroplasty through a meta-analysis. Methods: Data of studies published on EMBASE, PubMed, Web of Science and CENTRAL from inception to May 16, 2019 were collected for analysis. The primary outcomes were the frequencies of postoperative complications (cardiac, pulmonary, neuropsychiatric, genitourinary and gastrointestinal complications), unplanned intensive care unit transfer and mortality of patients who received joint arthroplasty or revision joint arthroplasty. The present meta-analysis was conducted strictly following the PRISMA reporting guidelines. The random effects model was used to calculate the odds ratios and corresponding 95% confidence intervals. Begg's funnel plot was used to assess publication bias. A subgroup analysis was further performed to clarify the potential heterogeneity, explore the source of heterogeneity, and estimate the stability of the outcomes. Results: Nine studies were included in the final pooled analysis. SA patients with joint arthroplasty or revision joint arthroplasty had higher incidence of postoperative pulmonary complications with compared with those without (7.94% vs. 1.84%, OR=2.88, 95% CI=1.76-4.72,  $I^2=99\%$ ,  $P<0.0001$ ). The subgroup analysis revealed that the article types had no effect on the results. The sensitivity analysis confirmed the outcome stability. The inverted funnel plot suggested the presence of publication bias. In addition, SA was associated with significantly higher incidence of unplanned ICU transfer (6.16% vs. 3.02%, OR=2.36, 95% CI=1.47-3.81,  $I^2=38\%$ ,  $P=0.0004$ ) and mortality (0.24% vs. 0.16%, OR=1.57, 95% CI=1.06-2.33,  $P=0.02$ ). However, other postoperative complications in patients with SA, such as cardiac, neuropsychiatric (0.15% vs. 0.13%, OR=0, 95% CI=0-0,  $P=0.46$ ,  $I^2=47\%$ ), gastrointestinal (0.94% vs. 0.65%, OR=1.32, 95% CI=0.84-2.0,  $I^2=86\%$ ,  $P=0.23$ ) and genitourinary (2.06% vs. 1.11%, OR=0.88, 95% CI=0.30-2.63,  $I^2=97\%$ ,  $P=0.82$ ) complications, were not statistically significant. Conclusion: After joint arthroplasty or revision joint arthroplasty, SA patients have a higher risk of postoperative pulmonary complications and mortality than those without SA.

**Keywords:** Postoperative complication, sleep apnea, joint arthroplasty, revision joint arthroplasty

## Introduction

Sleep apnea (SA) is a breathing disorder that can easily be disregarded. It is defined as multiple cessations of respiration during sleep that induce partial arousals and interfere with sleep, which causes sleep fragmentation and hypoxemia, and gives rise to physiologic disorders and various comorbidities, including cardiovascular disease, hypertension, cerebral vascular disease, and so on [1, 2].

SA can be divided into three types: obstructive, central and mixed central-obstructive. The pre-

valence of obstructive sleep apnea (OSA) is approximately 1-4% in adults, and the mortality rate is 20% at four years after the diagnosis [3]. However, the impact of undiagnosed SA is greatly underestimated in some epidemiological studies [4]. SA is a social problem that is highly associated with cardiovascular diseases, pulmonary diseases, hypertension, daytime sleepiness, work-related injuries, and so on. Patients who underwent joint arthroplasty or revision joint arthroplasty are mostly older and obese [5, 6]. The incidence of SA in patients who received joint arthroplasty is high, and can reach up to 8.7% [7]. SA may serve as a risk



resolved by consensus through a third investigator. The following data were extracted from each study: last name of the first author, year of publication, study design, size of SA and control groups, diagnosis of SA, mean age, BMI, gender (male), surgical type, the incidence of complications and outcomes, unplanned ICU transfer and mortality (**Table 1**).

Cardiac complications were defined as myocardial infarction or myocardial ischemia, or arrhythmia; pulmonary complications were defined as aspiration pneumonia, acute respiratory distress syndrome, re-intubation, hypoxemia, pulmonary embolism (PE), atelectasis, or mechanical or non-invasive ventilation; neuropsychiatric complications were defined as delirium, confusion, or cerebrovascular disease; genitourinary complications were defined as urinary tract infection or acute renal failure; gastrointestinal complications defined as nausea, vomiting, or ileus.

### *Quality assessment*

Two investigators independently evaluated the quality of the included articles using the Newcastle-Ottawa Scale (NOS, range: 0-9 stars) [25]. Each study was scored based on selection, comparability, exposure and outcome. Studies with a NOS score of  $\geq 6$  stars were considered as high-quality studies. Low-quality studies were excluded.

### *Statistical analysis*

Revman 5.2 was used for the statistical analysis. Odds ratios and 95% confidence intervals were used to evaluate the association between SA and postoperative complications in patients who underwent joint arthroplasty or revision joint arthroplasty. The DerSimonian and Laird (D-L) methodology was used to pool the summary estimates [26]. For studies that did not report the actual number of complications, the percentages or available data were used to calculate the number of complications. Statistical heterogeneity across studies was measured using the  $I^2$  statistical method.  $I^2 < 40\%$  was considered as low heterogeneity,  $I^2 = 40\text{--}60\%$  was considered as moderate heterogeneity, and  $I^2 = 50\text{--}90\%$  was considered as substantial heterogeneity. Inverted funnels plots were used to evaluate for possible publication bias. A random effects model was used when hetero-

geneity is significant ( $P < 0.1$  or  $I^2 > 50\%$ ). A subgroup analysis was performed to clarify the potential heterogeneity. In order to further explore the origin of the heterogeneity and estimate the stability of the outcomes, one study was removed each time when the others were analyzed. A two-tailed  $P$ -value  $< 0.05$  indicated that the difference is statistically significant.

## **Results**

### *Search results*

A total of 2,236 articles published in the English language were identified in the initial search. After the screening, nine articles which met the inclusion criteria were included in the final analysis [7, 8, 11, 12, 14, 18-21]. The flow diagram for article selection is presented in **Figure 2**.

### *Study characteristics*

The 9 included studies reported at least one case of postoperative cardiac, pulmonary, neuropsychiatric, genitourinary, or gastrointestinal complication, unplanned ICU transfer, or mortality. Five articles were case-control studies, while the remaining articles were prospective or retrospective cohort studies. Patients in the present meta-analysis were divided into two groups: patients with SA and patients without SA. According to the results of the NOS scores, all studies were of middle or high quality (**Tables 2, 3**). The location of the joint arthroplasty included the hip, knee and shoulder. A total of 1,061,786 patients underwent primary joint arthroplasty, and 258,455 patients underwent revision joint arthroplasty.

After reviewing all the included articles, it was found that SA was diagnosed by ICD code in five articles, by PSG in two articles, by questionnaire in one article, and by nocturnal oximetry and PSG in one article.

### *Postoperative pulmonary complications*

Postoperative pulmonary complications were compared in patients with or without SA in the eight studies [7, 8, 11, 12, 14, 18, 20, 21]. The relationship between SA and postoperative pulmonary complication was reanalyzed using the random effects model ( $I^2 = 99\%$ ). After pooling the data, it was found that SA was significantly

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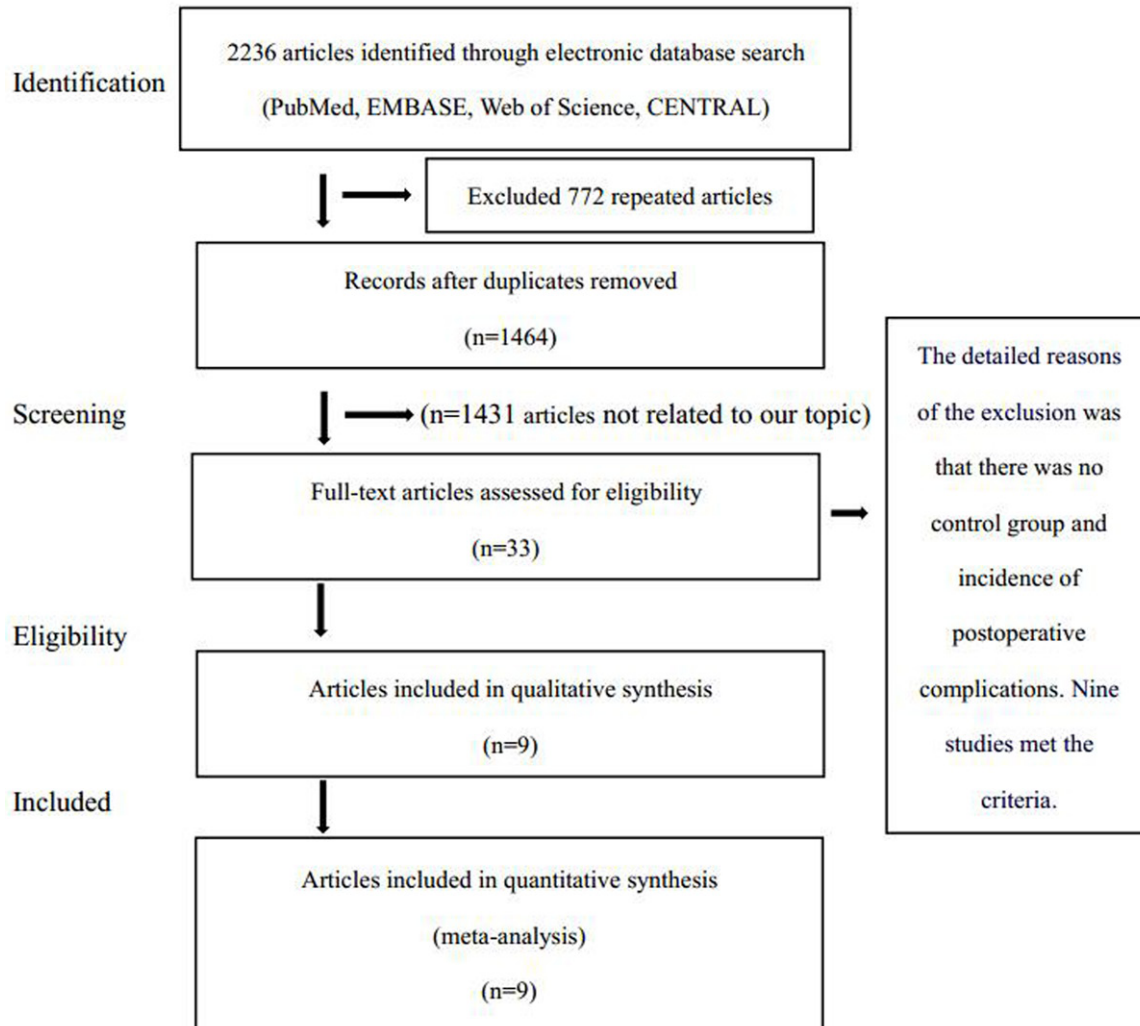
**Table 1.** Characteristics of articles included in the meta-analysis

Study	Design	Diagnosis of SA	Groups		Mean age (years)	BMI (kg/m²)	Male (%)	Surgical type	NOS score	Complications		
Gupta et al. 2001	Retrospective case-control	Nocturnal oximetry, PSG	OSA	101	68.1	33.5	69.3%	Hip or knee joint replacement	6 stars	Pulmonary complications	OSA	23
			Non-OSA	101	69.4	30.2	69.3%				Non-OSA	8
			Cardiac complications	OSA	16							
				Non-OSA	9							
			Neuropsychiatric complications	OSA	10							
				Non-OSA	3							
			Genitourinary complications	OSA	3							
				Non-OSA	7							
			Unplanned ICU transfer	OSA	20							
				Non-OSA	6							
Nepomnayshy et al. 2012	Retrospective case-control	PSG	OSA	72	63 in all	46.7 in all	27.2% in all	Total joint replacement	8 stars	Pulmonary complications	OSA	12
			Non-OSA	343							Non-OSA	14
			Cardiac complications	OSA						4		
				Non-OSA						17		
Berend et al. 2010	Retrospective cohort	Screening questions	OSA	109	63.0	38.4 in OSA, 31.2 in all	54.13% in OSA	Total joint arthroplasty	7 stars	Pulmonary complications	OSA	15
			Non-OSA	134	61.5						Non-OSA	4
			Neuropsychiatric complications	OSA	1							
				Non-OSA	1							
			Genitourinary complications	OSA	1							
				Non-OSA	0							
			Gastrointestinal complication	OSA	9							
				Non-OSA	3							
Naqvi et al. 2017	Retrospective case-control	ICD-9 or 10 code	OSA	1246	63.49	33.65	60.51% 60.54%	Total joint arthroplasty	8 stars	Pulmonary complications	OSA	21
			Non-OSA	3738	63.18	34.05					Non-OSA	21
			Cardiac complications	OSA	23							
				Non-OSA	77							
			Neuropsychiatric complications	OSA	9							
				Non-OSA	33							
			Gastrointestinal complication	OSA	12							
				Non-OSA	25							
			Mortality	OSA	4							
				Non-OSA	4							
D'Apuzzo et al. 2012	Retrospective case-control	ICD-9 code	OSA	16608	Adjusted for the confounders of age and gender		Revision total hip or knee arthroplasty	8 stars	Pulmonary complications	OSA	174	
			Non-OSA	241847						Non-OSA	1928	
			Cardiac complications	OSA					130			
				Non-OSA					2338			
			Neuropsychiatric complications	SA					19			
				Non-SA					340			

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											Genitourinary complications	OSA	40
												Non-OSA	1526
											Gastrointestinal complication	OSA	70
												Non-OSA	1270
											Mortality	SA	66
												Non-SA	483
Mentsoudis et al. 2011	Retrospective cohort	ICD-9 codes	SA	58538	63.11	Not reported	52.25%	Total joint arthroplasty	7 stars		Pulmonary complications	SA	3945
			Non-SA	175614	62.74		52.68%					Non-SA	4390
Griffin et al. 2013	Retrospective cohort	ICD-9 code	OSA	1983	66.06	Total 68.8	Total 40%	Total shoulder arthroplasty or hemiarthroplasty	7 stars		Pulmonary complications	OSA	20
			Non-OSA	31157	68.99							Non-OSA	284
											Cardiac complications	OSA	4
												Non-OSA	183
											Neuropsychiatric complications	OSA	2
												Non-OSA	50
											Genitourinary complications	OSA	10
												Non-OSA	164
											Gastrointestinal complications	OSA	6
												Non-OSA	82
											Mortality	OSA	2
												Non-OSA	52
Flink et al. 2012	Prospective cohort	PSG	OSA	15	70.3	36.1	53.3%	Knee joint replacement	8 stars		Neuropsychiatric complications	OSA	8
			Non-OSA	91	74							Non-OSA	19
Mentsoudis et al. 2014	Retrospective case-control	ICD-9 codes	SA	44246	63.36	Not reported	53.9%	Total hip or knee arthroplasty	7 stars		Pulmonary complications	SA	5545
			Non-SA	485843	66.96		37.3%					Non-SA	10589
											Cardiac complications	SA	4224
												Non-SA	31127
											Neuropsychiatric complications	SA	46
												Non-SA	560
											Genitourinary complications	SA	1245
												Non-SA	6741
											Gastrointestinal complication	SA	507
												Non-SA	3571
											Mortality	SA	85
												Non-SA	716
											Unplanned ICU transfer	SA	2713
												Non-SA	14647

Note: BMI: Body Mass Index; ICD: International Code Disease; ICU: Intensive Care Unit; NOS: Newcastle-Ottawa Scale; OSA: Obstructive Sleep Apnea; PSG: Polysomnography; SA: Sleep apnea.



**Figure 2.** The flow diagram for the article selection process.

associated with the increased prevalence of postoperative pulmonary complications (7.94% vs. 1.84%, OR=2.88, 95% CI=1.76-4.72,  $P<0.0001$ ; **Figure 3**). A subgroup analysis was performed to clarify the potential heterogeneity, and it was revealed that the article types had no effect on the results (**Figure 4**). The sensitivity analysis confirmed the stability of the outcomes. The inverted funnel plot was found to be asymmetrical at the middle and bottom, suggesting the presence of publication bias (**Figure 5**).

#### *Postoperative cardiac complications*

The results of six articles were included to compare the incidence of cardiac complications in patients with or without SA [8, 12, 14, 18, 20,

21]. The meta-analysis resulted in an OR of 1.01 (95% CI=0.66-3.56,  $I^2=92\%$ ,  $P=0.96$ ). Furthermore, these results revealed that the incidence of postoperative cardiac complication was not significantly higher in patients with SA, who underwent joint arthroplasty or revision joint arthroplasty (6.85% vs. 4.42%, **Figure 6**).

#### *Postoperative neuropsychiatric complications*

Seven studies reported the incidence of postoperative neuropsychiatric complications [7, 8, 12, 14, 18-20]. As shown in **Figure 7**, after the pooled analysis, the across line of the 95% CI intersected with an invalid vertical line (0.15% vs. 0.13%, OR=0, 95% CI=0-0,  $P=0.46$ ,  $I^2=47\%$ ). This shows that the incidence of postop-



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**Table 2.** Quality assessment criteria through the Newcastle-Ottawa Scale (NOS) for case control studies

NOS criteria	Studies (year)				
	D'Apuzzo (2012)	Gupta et al. (2001)	Memtsoudis et al. (2014)	Naqvi SY et al. (2017)	Nepomhayetas (2013)
A. Selection (maximum of four stars)					
1. Is the case definition adequate	★	★	☆	★	★
2. Representativeness of the cases	★	★	★	★	★
3. Selection of Controls		☆	☆	☆	☆
4. Definition of Controls	★	★	★	★	★
B. Comparability (maximum of two stars)					
1. Comparability of cases and controls on the basis of the design or analysis	★★	★☆	★★	★★	★★
C. Exposure (maximum of three stars)					
1. Ascertainment of exposure	★	★	★	★	★
2. Same method of ascertainment for cases and controls	★	★	★	★	★
3. Non-response rate	★	★	★	★	★
Total (maximum of nine stars)	8	7	7	8	8

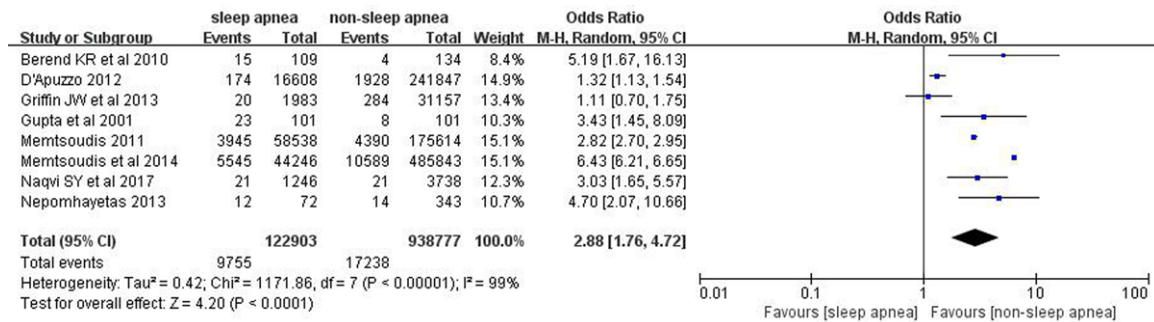
Note: NOS: Newcastle-Ottawa Scale. <https://doi.org/10.6084/m9.figshare.8180828.v1>

**Table 3.** Quality assessment criteria through the Newcastle-Ottawa Scale (NOS) for cohort studies

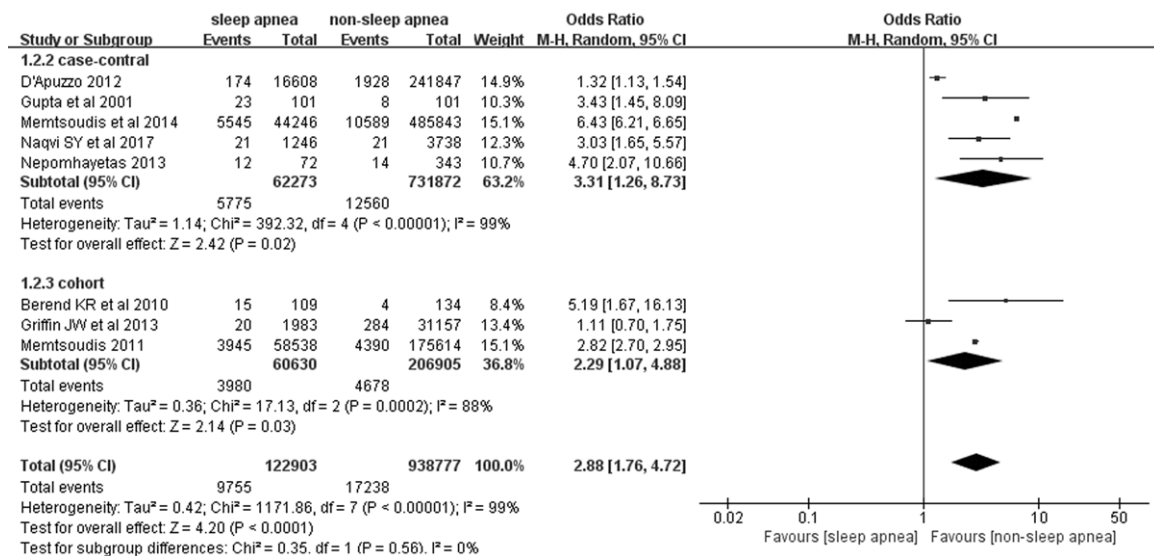
NOS criteria	Studies (year)		
	Berend KR et al. (2010)	Griffin JW et al. (2013)	Memtsoudis (2011)
A. Selection (maximum of four stars)			
1. Representativeness of the exposed cohort	★	★	★
2. Selection of the non-exposed cohort	★	★	★
3. Ascertainment of exposure	★	☆	★
4. Demonstration that outcome of interest was not present at start of study (no bone disease at start of study)	★	★	★
B. Comparability (maximum of two stars)			
1. Comparability of cohort on the basis of the design or analysis	★☆	★☆	★☆
C. Outcome (maximum of three stars)			
1. Assessment of outcome	★	★	★
2. Was follow-up long enough for outcomes to occur	★	★	☆
3. Adequacy of follow-up of cohorts	★	★	★
Total (maximum of nine stars)	8	7	7

Note: NOS: Newcastle-Ottawa Scale. <https://doi.org/10.6084/m9.figshare.8180831.v1>

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**Figure 3.** Outcomes for the random effects meta-analysis on the relationship between SA and postoperative pulmonary complications.



**Figure 4.** The outcome of the subgroup analysis revealed similar outcomes.

erative neuropsychiatric complications in patients with SA was not statistically significant.

### Postoperative gastrointestinal complications

Five studies reported the incidence of postoperative gastrointestinal complications [7, 12, 14, 18, 20]. As shown in **Figure 8**, the diamond pattern was intersected by an invalid vertical line after the pooled analysis (0.94% vs. 0.65%,  $OR = 1.32$ , 95%  $CI = 0.84-2.0$ ,  $I^2 = 86\%$ ,  $P = 0.23$ ). This reveals that the incidence of postoperative gastrointestinal complications in patients with SA was not statistically significant.

### Postoperative genitourinary complications

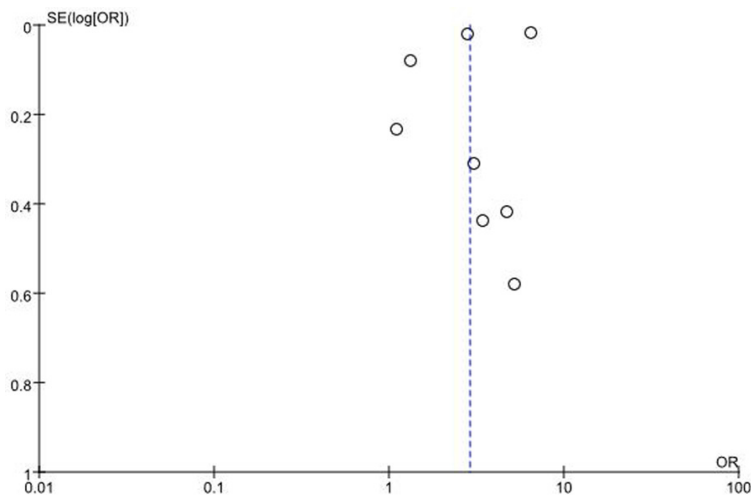
Five studies reported the incidence of postoperative genitourinary complications [7, 8, 12, 14, 18]. The diamond pattern was intersected

by an invalid vertical line after the pooled analysis (2.06% vs. 1.11%,  $OR = 0.88$ , 95%  $CI = 0.30-2.63$ ,  $I^2 = 97\%$ ,  $P = 0.82$ ). This reveals that the incidence of postoperative genitourinary complications was not significantly higher in patients with SA when compared to those without (**Figure 9**).

### Unplanned ICU transfer

Two studies reported the incidence of unplanned ICU transfer [8, 14]. The results showed that after joint arthroplasty or revision joint arthroplasty, a significantly higher incidence of unplanned ICU transfer happened in patients with SA when compared with those without (6.16% vs. 3.02%,  $OR = 2.36$ , 95%  $CI = 1.47-3.81$ ,  $I^2 = 38\%$ ,  $P = 0.0004$ ), but there was low heterogeneity (**Figure 10**). The sensitivity analysis





**Figure 5.** The inverted funnel plot was found to be asymmetrical at the middle and bottom, suggesting publications bias.

sis, subgroup analysis and publication bias assay were not performed, because merely two studies were included.

## Mortality

Four studies reported the incidence of mortality [12, 14, 18, 20]. The meta-analysis of the data obtained from these studies revealed a higher mortality for patients with SA when compared with those without (0.24% vs. 0.16%, OR=1.57, 95% CI=1.06-2.33, P=0.02; **Figure 11**). However, there was moderate heterogeneity ( $I^2=65\%$ ). Publication bias and subgroup analyses were not performed, because only four studies were included in the present meta-analysis.

## Discussion

To our knowledge, the present study was the first to conduct a meta-analysis to explore the relationship between SA and postoperative complications after joint arthroplasty or revision joint arthroplasty. Compared with previous meta-analyses, our meta-analysis supports that SA patients have an increased risk of postoperative mortality, which is a critical finding that shouldn't be ignored.

PSG is the gold standard for the diagnosis of SA. In one article, the diagnosis of OSA was confirmed by questionnaire [7]. In another article, the diagnosis of OSA in 84 patients was confirmed by PSG, while the remaining 17 patients had highly abnormal overnight oxime-

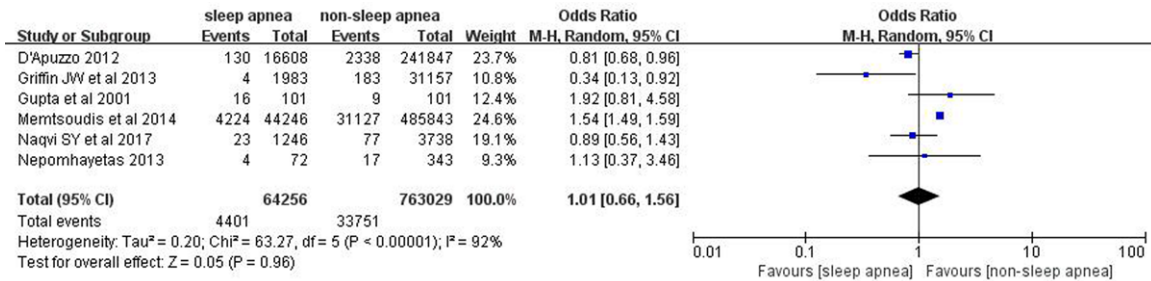
try, which was consistent with OSA. In addition, 17 patients with abnormal oximetry also had a clinical history and examination findings compatible with OSA, including habitual snoring and observed apneic episodes [8]. Patients must have severe SA when apneic episodes were observed. Therefore, the diagnosis of SA or OSA was the same, and did not affect the findings.

Among the nine included studies, two studies reported only one postoperative complication [11, 19]. In these two studies, one study prospectively evaluated the association between

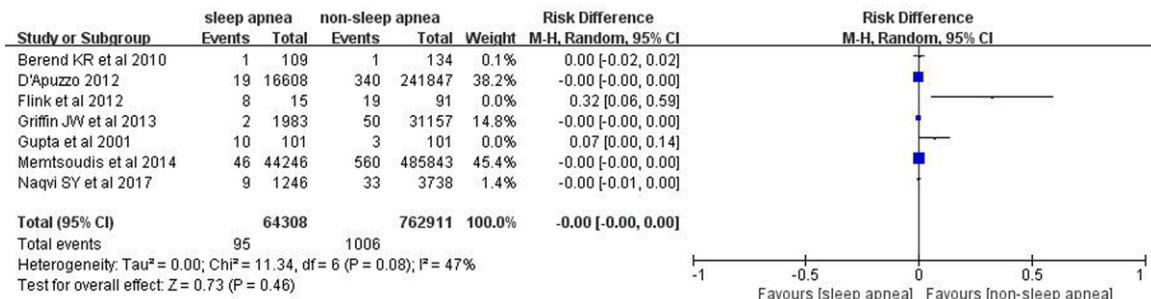
postoperative delirium and OSA in patients ( $\geq 65$  years old) received primary total knee arthroplasty [19]. After adjusting the multiple logistic regressions for the effects of covariates, OSA was the only significant risk factor for postoperative delirium. This was the only study that supported OSA as a significant independent predictor for postoperative neuropsychiatric complications in the present meta-analysis. A total of seven studies were included to analyze the association between SA and postoperative neuropsychiatric complications, including delirium, confusion and cerebrovascular disease [7, 8, 12, 14, 18-20]. We found that an increased risk of postoperative neuropsychiatric complications was noted in patients with SA when compared to patients without SA, but the difference was insignificant.

This study retrospectively evaluated the association between postoperative pulmonary complications and SA in patients undergoing lower-extremity joint arthroplasty. After matching one patient with SA to three patients without SA, and adjusting the multivariable logistic regressions for the effects of covariates, it was found that SA is an independent risk factor for postoperative pulmonary complications [7, 8, 11, 12, 14, 20, 21]. Conversely, Griffin et al. did not support the finding that OSA could significantly increase any of the perioperative complications as well as the mortality after the multivariate analysis [18]. However, this study supported the finding that OSA can significantly decrease postoperative cardiac complications, which is

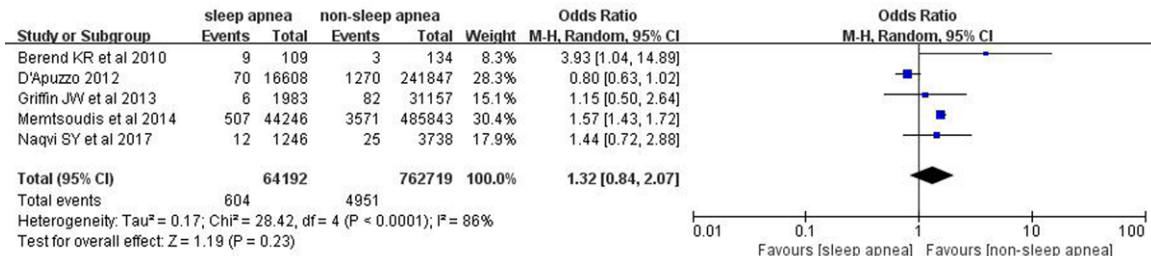
## Sleep apnea for postoperative complications



**Figure 6.** Outcomes for the random effects meta-analysis on the relationship between SA and postoperative cardiac complications.



**Figure 7.** Outcomes for the random effects meta-analysis on the relationship between SA and postoperative neuro-psychiatric complications.



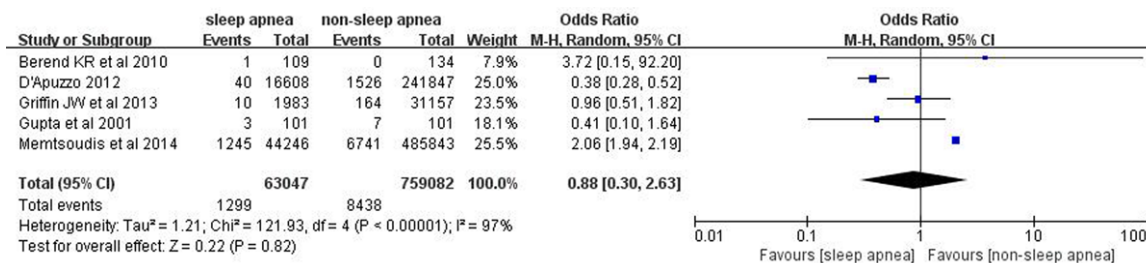
**Figure 8.** Outcomes for the random effects meta-analysis on the relationship between SA and postoperative gastro-intestinal complications.

opposite to the conclusion in the present study.

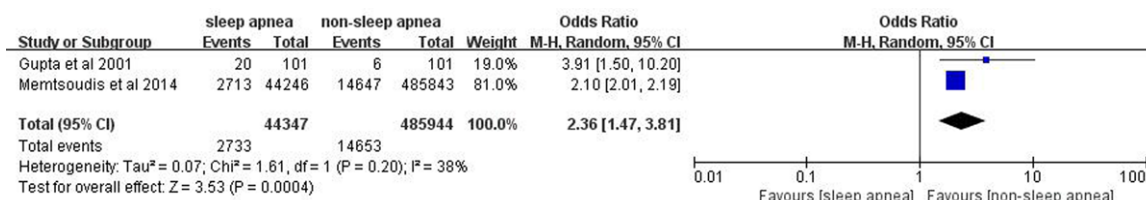
Six studies were included to analyze the association between SA and postoperative cardiac complications [8, 12, 14, 18, 20, 21]. Increased postoperative cardiac complications were noted in patients with SA when compared with patients without SA, but the difference was not statistically significant. However, one study reported that SA served as a significant independent risk factor for postoperative cardiac complications after performing a multivariate analysis [14].

Two studies all supported the finding that SA is a significant independent risk factor for postoperative unplanned ICU transfer, and this result was the same as that of the present conclusion [8, 14]. However, the number of included studies was too small and the results may be misleading, and the pooled analysis may have no statistical meaning. Hence, this possibility cannot be overlooked due to the potential consequences. At the same time, the results of the present meta-analysis support the finding that SA is a significant independent risk factor for postoperative mortality. Among the four studies included in present meta-anal-

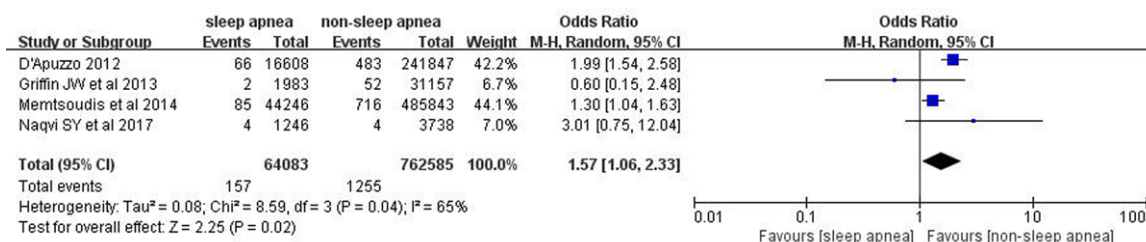
## Sleep apnea for postoperative complications



**Figure 9.** Outcomes for the random effects meta-analysis on the relationship between SA and postoperative genitourinary complications.



**Figure 10.** Outcomes for the random effects meta-analysis on the relationship between SA and postoperative unplanned ICU transfer.



**Figure 11.** Outcomes for the random effects meta-analysis on the relationship between SA and postoperative mortality.

ysis, two studies supported the present conclusion, while the remaining two studies were not statistically significant, and none of these studies opposed the present results [12, 14, 18, 20].

In the present meta-analysis, an increased risk of postoperative gastrointestinal complications, including nausea, vomiting and ileus, was noted in patients with SA when compared with patients without SA, but the difference was not statistically significant. This result was supported by four studies [7, 12, 18, 20]. However, one study supported the finding that SA is a significant independent risk factor for gastrointestinal complications [14].

One study reported that SA is a significant independent risk factor for postoperative genitourinary complications [14]. However, another st-

udy found that SA could significantly decrease the incidence of postoperative genitourinary complications [12]. In the present meta-analysis, increased risk of postoperative genitourinary complications, including urinary tract infection and acute renal failure, was noted in patients with SA compared with patients without SA, but the difference was not statistically significant. These present results were supported by the other three studies [7, 8, 18].

Overall, the major significant findings of the present meta-analysis were that after joint arthroplasty or revision joint arthroplasty, patients with SA have a high risk of postoperative pulmonary complications and mortality, which are consistent with the conclusion of most of the included studies, suggesting that SA is a neglected and potentially fatal risk factor in patients with joint arthroplasty or revision joint

arthroplasty. Interventions should be actively performed and nursing should be strengthened during the hospitalization, in order to reduce postoperative complications.

This meta-analysis also has some limitations. First, most of the included studies were retrospective studies. Hence, selection bias could easily occur. Second, although the present study strictly followed the PRISMA guidelines, and the random effects model was used to calculate the odds ratios and corresponding 95% confidence intervals, some of the important results of the included studies were substantially heterogeneous. In addition, although the sensitivity analysis confirmed the stability of the outcomes, a subgroup analysis was not performed due to the small number of included studies in some pooled analyses. Third, since one postoperative complication includes many types of diseases, the data pools may lead to heterogeneity.

In conclusion, SA was associated with high risk of postoperative pulmonary complication and mortality in patients with SA or without SA after joint arthroplasty or revision joint arthroplasty.

## Disclosure of conflict of interest

None.

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