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## **BMJ Open**

## Association of obstructive sleep apnea with the risk of vascular outcomes and total mortality: a meta-analysis

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### **BMJ Open**

Association of obstructive sleep apnea with the risk of vascular outcomes and total mortality: a meta-analysis

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### Abstract

Objective: This study aimed to conduct a meta-analysis to explore and summarize the evidence regarding the association between obstructive sleep apnea (OSA) and the subsequent risk for vascular outcomes and total mortality.

Methods: Electronic databases PubMed, EmBase, and the Cochrane Library were searched to identify studies conducted through May 2016. Prospective cohort studies that reported effect estimates with 95% confidence intervals of major adverse cardiac events (MACEs), coronary heart disease (CHD), stroke, cardiac death, total mortality, and heart failure for different levels versus the lowest level of OSA were included.

Results: A total of 16 cohort studies reporting data on 36,363 individuals were included. Severe OSA was associated with a greater risk of MACEs (P < 0.001), CHD (P = 0.003), stroke (P < 0.001), cardiac death (P = 0.003), and total mortality (P < 0.003)0.001); moderate OSA had a harmful impact on MACEs (P = 0.034) and CHD (P =(0.026); and no significant association was found between mild OSA and the risk of vascular outcomes or total mortality (P > 0.05). Finally, no evidence of a factor-specific difference in the risk ratio for MACEs among participants with different levels of OSA compared with those with the lowest level of OSA was found. Conclusions: This study indicated that severe and moderate OSA were associated with an increased risk of vascular outcomes and total mortality. This relationship might differ between genders. Therefore, further large-scale prospective studies are needed

to verify this difference.

Key words: meta-analysis; mortality, obstructive sleep apnea, vascular outcome

### **Article Summary:**

Strengths and limitations of this study

1. Degree of association of OSA to fatal and non-fatal CDs is gender specific.

2. Statistical evidence on association of moderate-to-severe OSA with MACEs.

3. Peculiar study design assesses risk-ratios as per patient characteristics.

4. Quantitative data to emphasize association of OSA as a poignant factor for CDs.

### Introduction

Obstructive sleep apnea (OSA) affects 24% of middle-aged men and 9% of women in the USA, but daytime sleepiness was reported in 17% and 22% of these subjects, respectively[1]. OSA is an increasingly prevalent condition characterized by repetitive obstruction of the upper airway during sleep accompanied by episodic hypoxia, arousal, and sleep fragmentation[2]. Previous studies suggest that OSA was associated with increased risk of glaucoma, diabetic kidney disease, and metabolic syndrome[3-5]. However, data on the association between OSA and the risk of subsequent vascular outcomes and mortality are both limited and inconclusive. Furthermore, whether these relationships differ according to the characteristics of patients with OSA also needs to be verified.

Several meta-analyses have illustrated that continuous positive airway pressure (CPAP) interventions aimed at OSA may reduce the risk of cardiovascular outcomes.

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Kim et al[6] showed that CPAP treatment for OSA was associated with a lower incidence of stroke and cardiac events. Furthermore, Bratton et al[7] indicated that among patients with OSA, use of both CPAP and mandibular advancement devices was associated with reductions in blood pressure. Nadeem et al[8] suggested that CPAP treatment for OSA seemed to improve dyslipidemia (decrease in total cholesterol and low-density lipoprotein, and increase in high-density lipoprotein), whereas it does not appear to affect the triglyceride levels. These studies recommend that patients with OSA who receive interventions have a reduced risk of cardiovascular diseases. Therefore, clarifying the relationship between OSA and vascular outcomes is particularly important as it has not been definitively determined. This study attempted to perform a large-scale examination of the available prospective studies to determine the association of OSA with the potential risk of vascular outcomes and total mortality.

### Methods

### Data sources, search strategy, and selection criteria

This study was conducted and reported according to the Meta-analysis of Observational Studies in Epidemiology protocol[9].

Any prospective cohort study that examined the relationship between OSA and vascular outcomes or total mortality was eligible for inclusion in this study, and no restrictions were placed on language or publication status (e.g., published, in press, or in progress). Electronic databases PubMed, EmBase, and the Cochrane Library were

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searched for articles published through May 2016, using the terms "sleep apnea" OR "obstructive sleep apneas" AND ("cardiovascular disease" OR "stroke" OR "cardiac death"OR "mortality" OR "death" OR "CVD" OR "myocardial infarction" OR "coronary events") AND "clinical trials" AND "human" as the search terms (Supplemental 1). Manual searches of reference lists were also conducted from all the relevant original and reviewed articles to identify additional eligible studies. The medical subject heading, methods, patient population, design, exposure, and outcome variables of these articles were used to identify the relevant studies.

The literature search was independently undertaken by two authors using a standardized approach. Any inconsistencies between these two authors were settled by the primary author until a consensus was reached. The study was eligible for inclusion if the following criteria were met: (1) the study had a prospective cohort design; (2) the study investigated the association between OSA and the risk of major adverse cardiac events (MACEs), coronary heart disease (CHD), stroke, cardiac death, total mortality, and heart failure; and (3) the authors reported effect estimates [risk ratio (RR), hazard ratio (HR), or odds ratio (OR)] and 95% confidence intervals (CIs) for comparisons of different levels of OSA versus lowest OSA level. All case-control studies were excluded because various confounding factors could bias the results.

### **Data Collection and Quality Assessment**

The data collected included the first author's name, publication year, country, sample size, mean age at baseline, percentage of male patients, body mass index

(BMI), disease status, assessment of OSA, follow-up duration, effect estimate and its 95% CI, reported endpoints, and covariates in the fully adjusted model. For studies that reported several multivariable adjusted RRs, the effect estimate that was maximally adjusted for potential confounders was selected.

The Newcastle–Ottawa Scale (NOS), which is quite comprehensive and has been partially validated for evaluating the quality of observational studies in the meta-analysis, was used to evaluate the methodological quality[10]. The NOS is based on the following three subscales: selection (4 items), comparability (1 item), and outcome (3 items). A "star system" (range, 0-9) was developed for assessment (Table 1). The data extraction and quality assessment were conducted independently by two authors. Information was examined and adjudicated independently by an additional author referring to the original studies.

### Statistical analysis

The relationship between OSA and risk of vascular outcomes or total mortality based on the effect estimate (OR, RR, or HR) and its 95% CI was examined in each study. To analyze the trend between OSA levels and vascular outcomes or total mortality risk, a semi-parametric method was first used to evaluate the association between mild OSA [apnea-hypopnea index (AHI): 5-15], moderate OSA (AHI: 15–30), severe OSA (AHI > 30), and the risk of vascular outcomes or total mortality[11]. Each category of AHI levels was established based on its calculated median, and the control category was composed of participants with lowest AHI or

normal participants in each study. Furthermore, when more than one median of AHI levels in each study was classified into one of these three categories, the fixed-effects model was used to calculate their summary RRs and 95% CIs for effect estimates of each category[12]. The random-effects model was then used to calculate summary RRs and 95% CIs for mild, moderate, and severe OSA versus normal[13]. Finally, the relative risk ratios and the corresponding 95% CIs were estimated using specific RRs and 95% CIs after considering the country, mean age, gender, BMI, disease status, and duration of the follow-up period[14].

Heterogeneity between studies was investigated using the Q-statistic, and P values <0.10 was considered as indicative of significant heterogeneity[15 16]. Subgroup analyses were conducted for mild, moderate, and severe OSA, and the risk of MACEs based on the country, mean age, gender, BMI, disease status, and duration of the follow-up period. A sensitivity analysis was also performed by removing each individual study from the meta-analysis[17]. Several methods were used to check for potential publication bias. Visual inspections of funnel plots for MACEs were conducted. The Egger[18] and Begg[19] tests were also used to statistically assess publication bias for MACEs. All reported P values were two sided, and P values <0.05 were considered statistically significant for all included studies. Statistical analyses were performed using the STATA software (version 12.0; Stata Corporation, TX, USA).

### Results

### Literature Search

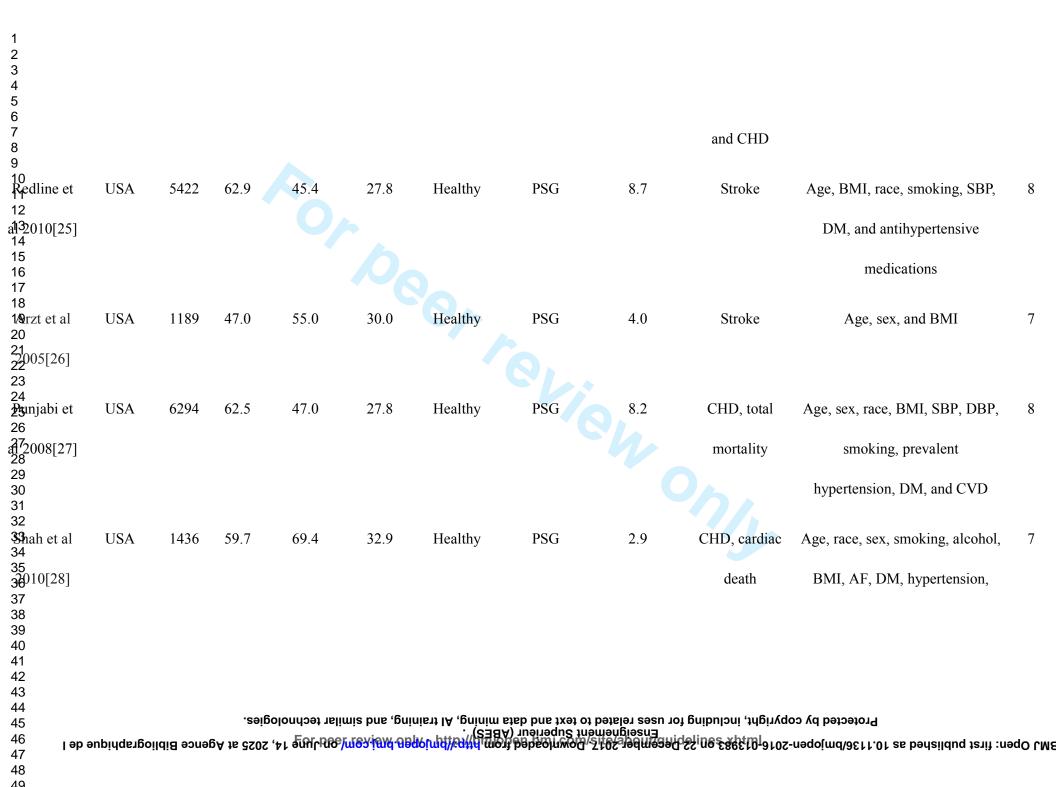
The results of study-selection process are shown in Figure 1. An initial electronic search yielded 3282 articles, of which 3236 duplicates and irrelevant studies were excluded, and 46 potentially eligible studies were selected. After detailed evaluations, 16 prospective studies were selected for the final meta-analysis[20-35]. No new studies qualified for inclusion after a manual search of the reference lists of these studies. The general characteristics of the included studies are presented in Table 1.

### Study Characteristics

Sixteen studies with a total of 36,363 individuals qualified for this study. The follow-up period for participants was 2.9-18.0 years, while 73-6294 individuals were included in each study. Eight studies were conducted in the USA, four in Spain, one in Sweden, one in Portugal, one in Hungary, and one in Canada. Furthermore, 11 studies reported healthy participants, and the remaining 5 studies reported participants with different diseases. The mean BMI ranged from 26.8 to 34.0 kg/m<sup>2</sup>. Fourteen studies used polysomnography (PSG), and the remaining one study used limited PSG to assess the levels of OSA. The study quality was assessed using the NOS (Table 1). Overall, one study had a score of 9, six studies had a score of 8, seven studies had a score of 7, and the remaining two studies had a score of 6.

1 2											
3 4											
5 6 7											
8 9			Ta	ble 1. Baseline	characteris	tic of studies	included in the	systematic revi	ew and meta-analy	y\$1\$	
10 11 <sup>Study</sup>	Country	Sampl	Mean	Percentage	BMI	Disease	Assessment	Follow-up	Reported	Adjusted factors	NOS
12 13 14		e size	age	male (%)		status	OSA	duration	outcomes		score
14 15 16							OSA	(year)			
17											
14900e et al 20		408	59.1	58.4	27.0	CAD	Limited	5.1	CHD, stroke,	Age, sex, BMI, hypertension,	7
$21 \\ 22 \\ 22 \\ 000 [20]$							PSG		total mortality	DM, LVF, and coronary	
23 24 25										intervention	
25 26 27		4400	( <b>2</b> , <b>4</b> )	42.5	28.2	TT 14h	DSC	8.7		Assess DML such as DM	0
27 Crottlieb et 28 29		4422	62.4	43.5	28.2	Healthy	PSG	8.1	CHD, HF	Age, race, BMI, smoking, DM,	8
al02010[21 31	]									SBP, DBP, TC, HDL-C,	
32 33 34										lipid-lowering medications, and	
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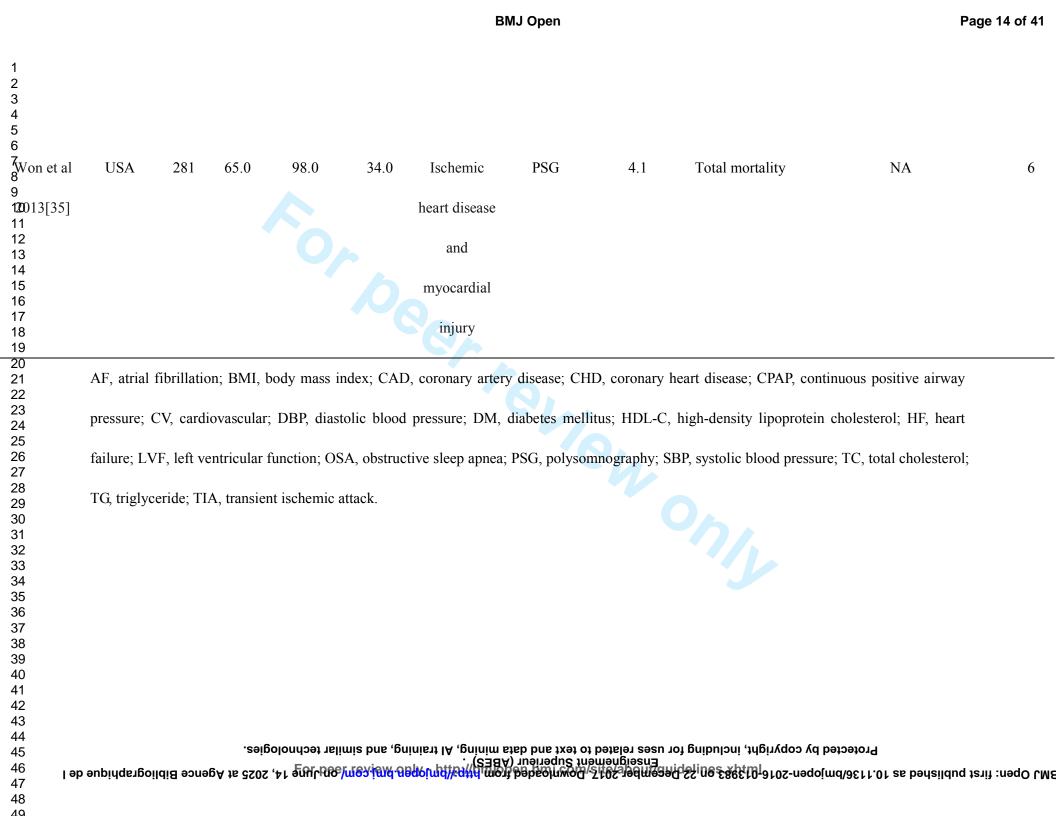
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Žampos-R	Spain	1116	56.1	0.0	36.6	Healthy	PSG	6.0	Cardiac death	Age, BMI, DM, hypertension,	8
9 <b>d0</b> riguez et 11 al <sup>2</sup> 2012[22]										and previous CVD	
14 15 Mgarin et al 17	Spain	1729	49.9	100	28.7	Healthy	PSG	10.1	Cardiac death	Age, diagnostic group, presence	9
18005[23] 19									and CHD	of CVD, DM, hypertension, lipid	
20 21 22										disorders, smoking, alcohol, SBP	
20 21 22 23 24 25 26 27										DBP, blood glucose, TC, TG, and	
25 26 27										use of antihypertensive,	
28 29										lipid-lowering and antidiabetic	
30 31 32 33										drugs	
Young et al	USA	1522	48.0	55.0	28.6	Healthy	PSG	18.0	Cardiac death,	Age, age-squared, sex, BMI, and	8
36 32008[24] 38 39									total mortality,	BMI-squared	
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7Munoz et 9 all02006[31] 11 12	Spain	1034	79.8	57.0	26.8	Healthy	PSG	6.0	Stroke	Sex	7
13eão et al 14 15 12016[32] 17 18 19 20	Portugal	73	62.4	75.0	27.6	Acute coronary syndrome	PSG	6.3	CHD	Sex	7
21 22 23 al42014[33] 25 26 27 28 29	Hungary	100	51.0	56.8	26.8	Kidney transplant recipients	PSG	6.3	Total mortality	Unadjusted	6
<b>Stor</b> ndzersk 31 32 33 <sup>a</sup> et al 34 35014[34] 36 37 38 39 40 41 42 43 44	Canada	10149	49.9 .:sai	62.0	30.1	Healthy	PSG	5.7	Total mortality	for paramount	7
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Page 13 of 41



The summary RRs showed that mild OSA was not associated with MACEs (RR: 0.98; 95% CI: 0.87–1.11; P = 0.741; Fig. 2 and Table 2). Furthermore, the pooled analysis results for moderate and severe OSA indicated that they had a harmful effect on the risk of MACEs (moderate: RR: 1.16; 95% CI: 1.01–1.33; P = 0.034; Fig. 3 and Table 2; severe: RR: 2.04; 95% CI: 1.56–2.66; P < 0.001; Fig. 4 and Table 2). Subgroup analysis for MACEs was conducted to minimize heterogeneity among the included studies and evaluate the relationship of OSA and MACEs in specific subpopulations (Table 3). Overall, participants with moderate OSA were associated with an increased risk of MACEs if individuals did not have other diseases (RR: 1.16; 95%CI: 1.01–1.33; P = 0.034). Furthermore, no significant association was found between severe OSA and MACEs if the study included only women (RR: 1.98; 95% CI: 0.64-6.06; P = 0.234); in other subsets, severe OSA was associated with increased risk of MACEs (Table 3). Finally, no evidence of a factor-specific difference was found in the RR for MACEs among participants with OSA compared with controls (Table 3).

Table 2. Summary of the relative risks of all outcomes evaluated

Outcomes	Mild OSA	P value	Moderate OSA	P value	Severe OSA	<i>P</i> value
MACEs	0.98 (0.87–1.11)	0.741	1.16 (1.01–1.33)	0.034	2.04 (1.56–2.66)	< 0.001
CHD	1.25 (0.95–1.66)	0.117	1.38 (1.04–1.83)	0.026	1.63 (1.18–2.26)	0.003

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	Stroke	1.29 (	0.69–2.41)	0.424	1.35 (	0.82-2.23)	0.245	2.15 (	1.42–3.24)	<0.00	<b>Page</b>
Ca	ardiac death	1.80 (	0.68–4.76)	0.236	1.11 (	0.53–2.35)	0.781	2.96 (	1.45–6.01)	0.003	;
То	tal mortality	1.26 (	0.77–2.07)	0.354	1.04 (	0.60–1.79)	0.895	1.54 (	1.21–1.97)	<0.00	Protected by copyright, including for uses
Н	eart failure	1.02 (	0.78–1.34)	0.868	1.07 (	0.74–1.54)	0.719	1.44 (	0.94–2.21)	0.097	l by copy
	CHD, C	oronar	y heart disea	ase; MA	CE, majo	or cardiovas	cular ev	ent; OSA	, obstructive		right, in
	sleep ap	nea.									ocluding
			Tab	le 3. Su	bgroup ar	alyses for N	<b>IACEs</b>				l for uses
ariable	Subgroup		Mild OSA	0	P value	Moderate	OSA	P value	Severe OS	A	P vated t
Country	USA		1.00 (0.85	-1.17)	0.977	1.14 (0.99	-1.32)	0.064	1.90 (1.35	-2.67)	<0.0%9
	Other		1.02 (0.19	-5.52)	0.982	1.44 (0.83	-2.50)	0.198	2.35 (1.52	-3.65)	d da <0.000 mi
	USA vs oth	er	0.98 (0.18	-5.32)	0.982	0.79 (0.45	-1.40)	0.422	0.81 (0.46	-1.41)	0.459 A
/lean age	≥60		0.96 (0.86	-1.08)	0.540	1.13 (0.97-	-1.33)	0.117	1.78 (1.23		l trainsing, 0.00 trains, 0.00
	<60		1.40 (0.73	-2.70)	0.315	1.51 (0.94	-2.41)	0.086	2.31 (1.64	-3.24)	and <0.09
	≥60 vs <60		0.69 (0.35	-1.33)	0.265	0.75 (0.46	-1.23)	0.252	0.77 (0.47-	-1.27)	0.30chnologies.
Gender	Male		0.92 (0.73	-1.15)	0.455	1.10 (0.85	-1.42)	0.449	1.81 (1.14	-2.89)	0.0192. 0.0192.
	Female		1.97 (0.47	-8.25)	0.353	1.36 (0.67-	-2.76)	0.399	1.98 (0.64	-6.06)	0.234
	Male	VS	0.47 (0.11	-1.99)	0.304	0.81 (0.38	-1.72)	0.581	0.91 (0.27-	-3.08)	0.885

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3 4 5	BMI	≥30	1.75 (0.88–3.49)	0.111	1.70 (0.94–3.07)	0.079	2.72 (1.80-4.10)	<0.001
6 7 8		<30	0.96 (0.86–1.07)	0.449	1.14 (0.99–1.31)	0.078	1.80 (1.36–2.38)	<0.001
9 10 11		≥30 vs <30	1.82 (0.91–3.66)	0.092	1.49 (0.81–2.74)	0.198	1.51 (0.92–2.49)	0.10 0.10
12 13 14	Disease	Healthy	1.00 (0.85–1.17)	0.977	1.16 (1.01–1.33)	0.034	2.12 (1.53–2.94)	<0.001
15 16 17 18	statues	Other	1.02 (0.19–5.52)	0.982	-	-	1.96 (1.01–3.81)	Protected by 90 pyright, including for uses 0.839 0.839 for uses
19 20		Healthy vs	0.98 (0.18–5.32)	0.982	-	-	1.08 (0.52–2.27)	0.83 <b>5</b>
21 22 23 24		Other						Ense or uses r
25 26	Follow-up	≥6	0.96 (0.86–1.07)	0.449	1.14 (0.99–1.31)	0.064	2.06 (1.43-2.95)	<0.000 t
27 28 29	duration	<6	1.75 (0.88–3.49)	0.111	1.74 (0.87–3.49)	0.120	2.10 (1.39–3.17)	ntSupe ote9tar
30 31 32 33		≥6 vs <6	0.55 (0.27–1.10)	0.092	0.66 (0.32–1.33)	0.242	0.98 (0.57–1.70)	nd data mi 0.94a mi
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OSA, obstructive sleep apnea.

### **OSA** and CHD risk

The pooled data of meta-analysis showed that mild OSA was not associated with the risk of CHD (RR: 1.25; 95% CI: 0.95–1.66; P = 0.117; Table 2), whereas moderate OSA (RR: 1.38; 95% CI: 1.04–1.83; P = 0.026; Table 2) and severe OSA (RR: 1.63; 95% CI: 1.18–2.26; P = 0.003; Table 2) were associated with a significantly increased risk of CHD. Stratified analyses according to gender was conducted for different levels of OSA versus normal group, and it was found that patients with severe OSA had significantly increased risk of CHD in men (RR: 1.65;

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Table 4	Gender	difference	for	other	outcomes
	Genuer	unificience	101	other	outcomes

			BMJ	Open			Page 1
	95% CI: 1.06	6–2.57; <i>P</i> = 0.027).	No other s	significant differenc	es were det	ected (Table	Page Protected by copyright, including for uses related to wat and wat amining 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
	4).						
		Table 4. Ge	nder diffe	rence for other outc	omes		Protecte
Outcome	Subgroup	Mild OSA	P value	Moderate OSA	P value	Severe OSA	d by co
							vatont,
CHD	Men	0.93 (0.72–1.21)	0.596	1.09 (0.80–1.48)	0.582	1.65 (1.06–2.57)	inc <mark>2</mark> 7 0. <b>2</b> 2din
	Women	1.92 (0.43-8.64)	0.394	1.51 (0.38–5.97)	0.559	1.10 (0.12–9.87)	g fog33 0.9533 E
	Men vs women	0.48 (0.11–2.22)	0.351	0.72 (0.18–2.96)	0.651	1.50 (0.16–14.22)	ss relater
Stroke	Men	1.86 (0.67–5.14)	0.232	1.86 (0.70-4.95)	0.214	2.86 (1.10-7.41)	d to Southand
	Women	1.34 (0.76–2.36)	0.311	1.20 (0.67–2.15)	0.542	1.21 (0.65–2.25)	and data
	Men vs women	1.39 (0.43–4.45)	0.581	1.55 (0.50–4.84)	0.451	2.36 (0.76–7.38)	mining,
Cardiac	Men	_	_	1.15 (0.41–3.23)	0.791	2.87 (1.13–7.27)	Al tr26
death	Women	_	_	0.94 (0.19–4.61)	0.939	3.71 (0.41–33.87)	ig, a,245 0.245 s,
	Men vs women	_	_	1.22 (0.18-8.17)	0.935	0.77 (0.07–8.49)	imila34
Total	Men	_	_	_	-	1.72 (1.22–2.43)	:hno@02 0.@02
mortality	Women	_	_	_	_	3.50 (1.23–9.97)	ې 0.019
	Men vs women	_	_	_	_	0.49 (0.16–1.48)	0.206
Heart	Men	0.88 (0.57–1.35)	0.561	1.13 (0.68–1.88)	0.639	1.58 (0.93–2.67)	0.206

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Page <sup>·</sup>	19 of 41			BMJ	Open			3MJ Open
1 2 3 4	failure	Women	1.13 (0.80–1.60)	0.493	1.01 (0.60–1.70)	0.970	1.19 (0.56–2.52)	BMJ Open: first published as 10.1/136/bmjopen-2016-013983 on 22 0.545 Protected by copyright, including t
5 6 7 8		Men vs women	0.78 (0.45–1.35)	0.376	1.12 (0.54–2.32)	0.762	1.33 (0.53–3.33)	0.545 <b>s</b>
9 — 10 11		CHD, corona	ry heart disease; OS	A, obstru	active sleep apnea.			).1/136/bmjopen-2016-013983 on 22 December 2017 Enseignem Protected by copyright, including for uses related
12 13 14		OSA and stre	oke risk					jopen-20 by copy
15 16 17		Pooled ana	lysis results indicate	ed no ass	ociation between mil	d OSA (R)	R: 1.29; 95%	16-01398 right, inc
18 19 20 21					OSA (RR: 1.35; 95			
22 23 24		,			was associated wit < 0.001). Subgroup a			December 2017. D Enseignement or uses related to
25 26 27		× ×			harmful effect on the	2		_ @ . <sup>¬</sup>
28 29 30		(RR: 2.86; 95	5% CI: 1.10–7.41; <i>P</i>	= 0.031;	Table 4).			Downloaded nt Superieur o text and da
31 32 33		OSA and car	diac death risk					ed from ur (ABES data min
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40 47 48 49		death in men	(RR: 2.87; 95% CI:	1.13–7.2	27; $P = 0.026$ ; Table 4	4).		14, 2025 ɔlogies.
50 51		OSA and tot	al montality vish					at Ag

### **OSA** and total mortality risk

No significant association was found between mild OSA (RR: 1.26; 95% CI: 0.77–2.07; P = 0.354), moderate OSA (RR: 1.04; 95% CI: 0.60–1.79; P = 0.895), and

total mortality risk. However, severe OSA had a harmful impact on total mortality (RR: 1.54; 95% CI: 1.21–1.97; P < 0.001; Table 2). Stratified analysis suggested that severe OSA increased the risk of total mortality in men (RR: 1.72; 95% CI: 1.22–2.43; P = 0.002) and women (RR: 3.50; 95% CI: 1.23–9.97; P = 0.019; Table 4).

### **OSA** and heart failure risk

The summary results indicated no significant differences between mild OSA (RR: 1.02; 95% CI: 0.78–1.34; P = 0.868), moderate OSA (RR: 1.07; 95% CI: 0.74–1.54; P = 0.719), severe OSA (RR: 1.44; 95% CI: 0.94–2.21; P = 0.097), and the risk of heart failure (Table 2). Subgroup analysis reported similar results compared with the overall analysis.

### **Publication bias**

Review of the funnel plots could not rule out the potential publication bias for MACEs (Fig. 5). The Egger and Begg test results showed no evidence of publication bias for MACEs of mild OSA (*P* value for Egger: 0.132; *P* value for Begg: 0.221) and moderate OSA (*P* value for Egger: 0.052; *P* value for Begg: 0.452). Although the Begg test showed no evidence of publication bias for MACEs of severe OSA (*P* = 0.118), the Egger test showed potential evidence of publication bias for MACEs of severe OSA (*P* < 0.001). The conclusion did not change after adjustment for publication bias using the trim-and-fill method[36].

### Discussion

The present study was based on prospective cohort studies and explored all possible

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correlations between OSA and the outcomes of MACEs, CHD, stroke, cardiac death, total mortality, and heart failure. This large quantitative study included 36,363 individuals from 16 prospective cohort studies with a broad range of populations. The findings from the present meta-analysis suggested that mild OSA had no significant impact on the risk of vascular outcomes and total mortality, moderate OSA was associated with an increased risk of MACEs and CHD, and severe OSA had a harmful effect on the risk of MACEs, CHD, stroke, cardiac death, and total mortality.

A previous meta-analysis suggested that OSA was associated with stroke, but the relationship with ischemic heart disease and cardiovascular mortality needs further research[37]. However, this study could not illustrate the impact of different levels of OSA on the risk of serious cardiovascular outcomes. Further, Dong et al suggested that moderate-to-severe OSA significantly increased the risk of cardiovascular diseases, in particular, the risk of stroke[38]. Similarly, Ge et al indicated that severe OSA is a strong independent predictor of cardiovascular and all-cause mortality. CPAP treatment was associated with decreased cardiovascular mortality[39]. However, these two studies could not evaluate the association of OSA with the risk of vascular outcomes and total mortality in specific subpopulations. Finally, Wang et al suggested that severe OSA significantly increased the risk of CHD and stroke, and all-cause mortality. A positive association with CHD was observed for moderate OSA but not for mild OSA[40]. However, whether this relationship differs according to the characteristics of participants remains unclear. Therefore, a comprehensive meta-analysis of these prospective cohort studies was performed to evaluate any

possible correlates between OSA and vascular outcomes.

No significant difference was observed between mild OSA and the risk of vascular outcomes. However, several studies included in this study reported inconsistent results. Young et al suggested that mild OSA significantly increased the risk of CHD by 92%[24], whereas Punjabi et al indicated that mild OSA might have a harmful effect on the risk of CHD[27]. This might be because these two studies used healthy individuals as controls, which may make them more susceptible to acquired significant conclusion. Furthermore, most of these studies did not take into account potential confounders for the risk of cardiovascular disease. Moderate-to-severe OSA might play an important role in the risk of vascular outcomes. Shah et al concluded that OSA increased the risk of coronary events or death from cardiovascular causes[28]. Nearly all included studies reported adverse outcomes for severe OSA. Previous studies indicated that OSA was a cause of diabetes, which was an independent risk factor for MACEs. Multiple adjusted models might be biased as the adjusted variables are different, reflecting either mediation or confounding.

Subgroup analyses reported similar conclusions. Gender might have an impact on the relationship between OSA and CHD, stroke, or cardiac death, although the sex difference was not statistically significant. The possible reasons could be the lower prevalence of severe OSA in women and the later age of onset of OSA in women than in men. Furthermore, OSA in women always occurred after menopause. Physiological response to OSA is another reason for this nonsignificant difference. Finally, these conclusions might be unreliable because smaller cohorts were included in each subset.

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Therefore, further large-scale studies were needed to verify this difference. Therefore, a relative result was given and a synthetic and comprehensive review was provided.

Three strengths of this study should be highlighted. First, only prospective studies were included, which eliminated selection and recall bias, and could be of concern in retrospective case–control studies. Second, the large sample size allowed us to quantitatively assess the association of OSA with the risk of vascular outcomes and mortality, and thus the findings were potentially more robust than those of any individual study. Third, the summary RRs were calculated to evaluate any potential difference between subsets according to the characteristics of participants.

The limitations of this study were as follows: (1) the adjusted models were different across the included studies, and these factors might have played an important role in the development of vascular outcomes; (2) in a meta-analysis of published studies, publication bias was an inevitable problem; and (3) the analysis used pooled data (individual data were not available), which restricted performing a more detailed relevant analysis and obtaining more comprehensive results.

The results of this study suggest that moderate-to-severe OSA might play an important role in the risk of vascular outcomes, especially for men. Future studies should focus on specific populations to analyze the gender difference to study the association between OSA and vascular outcomes.

### **Author Contributions:**

Chengjuan Xie carried out the studies, participated in collecting data, and drafted the

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manuscript. Ruolin Zhu performed the statistical analysis and participated in its design. Yanghua Tian, Kai Wang helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of interests: All authors declare that they have no conflict of interest.

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Data sharing statement : No additional data available.

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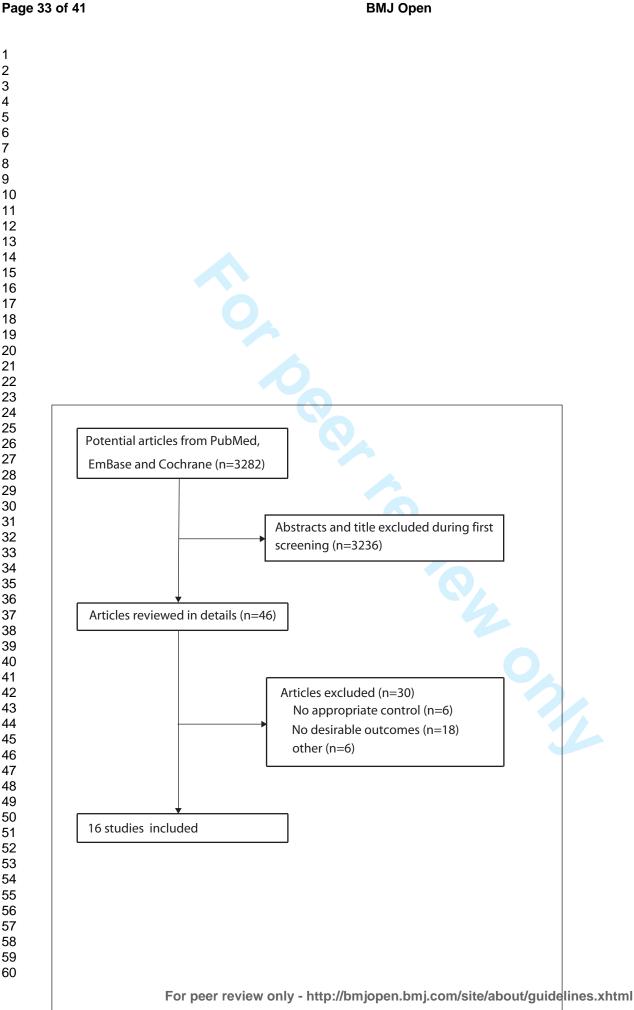
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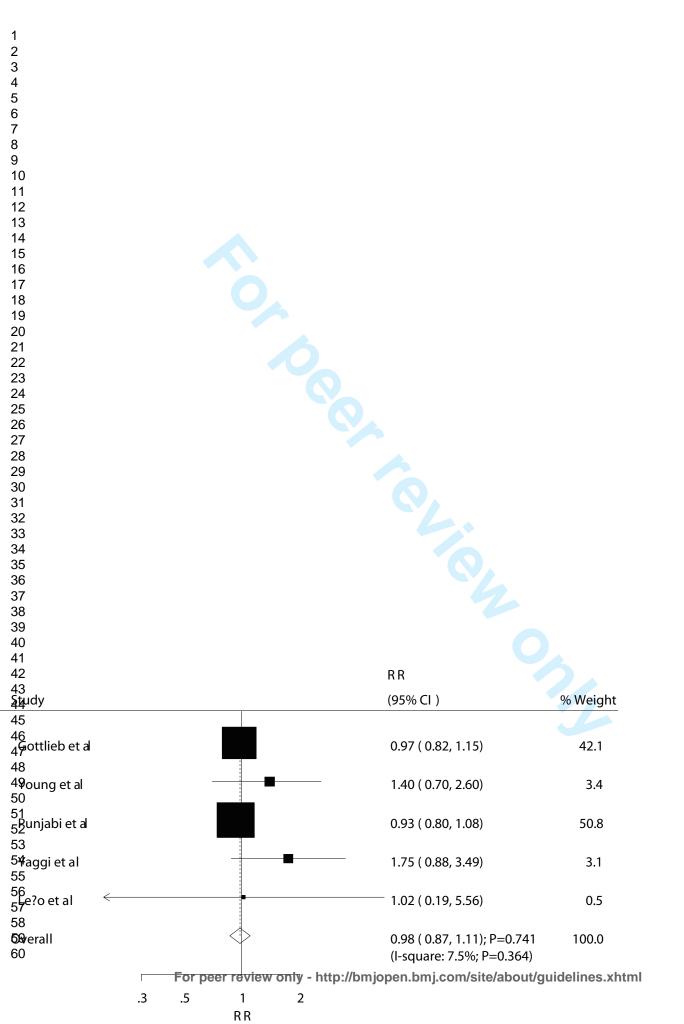
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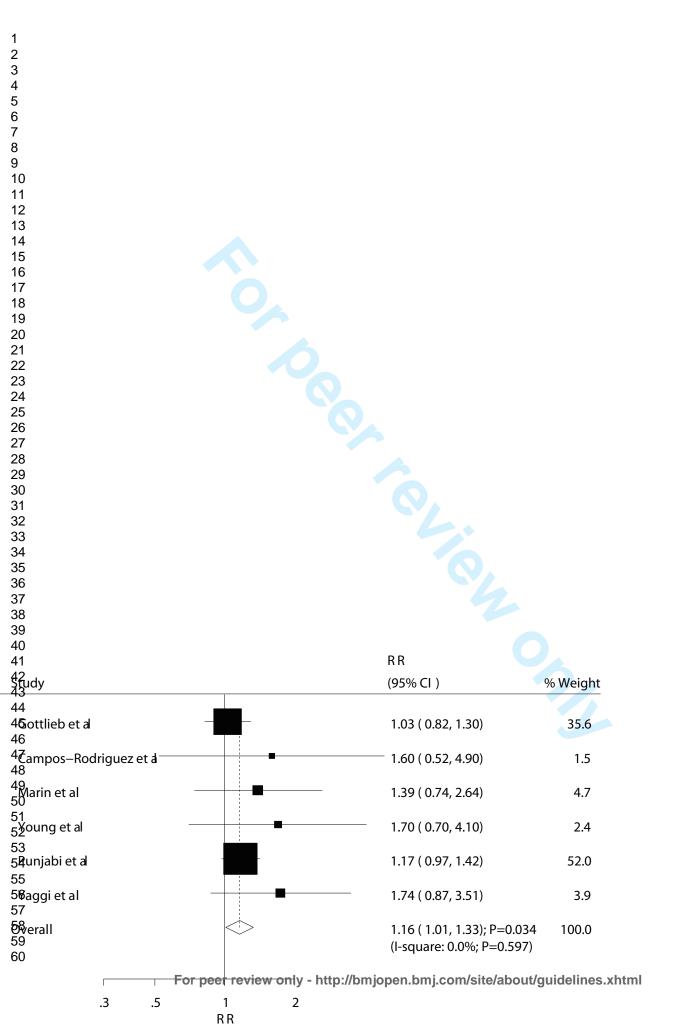
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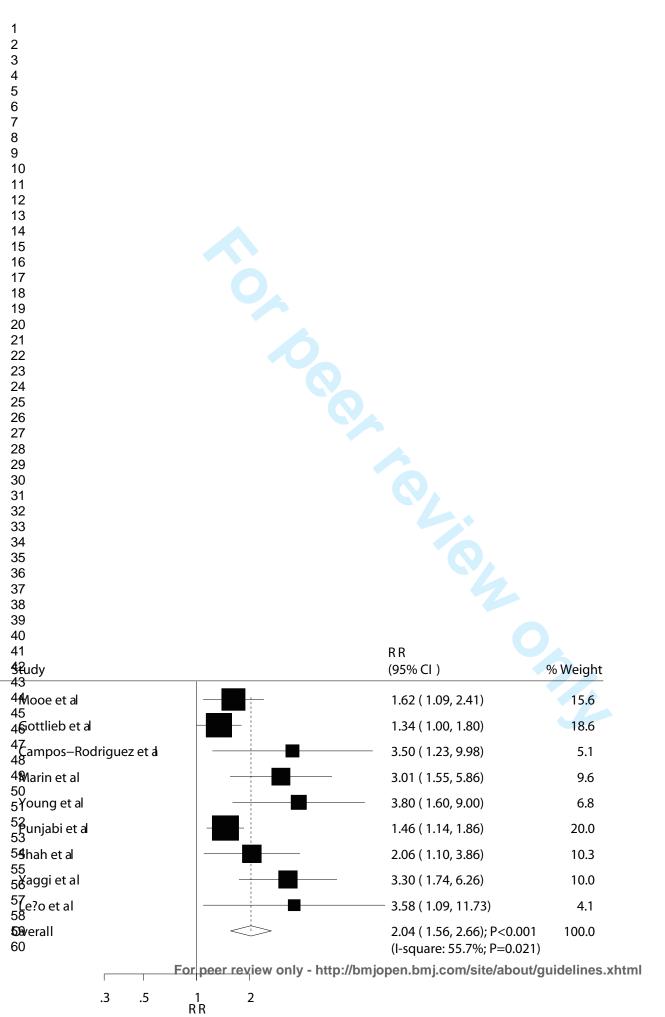
- Figure 1. Study selection process
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- Figure 3. Association between moderate OSA and MACEs
- Figure 4. Association between severe OSA and MACEs

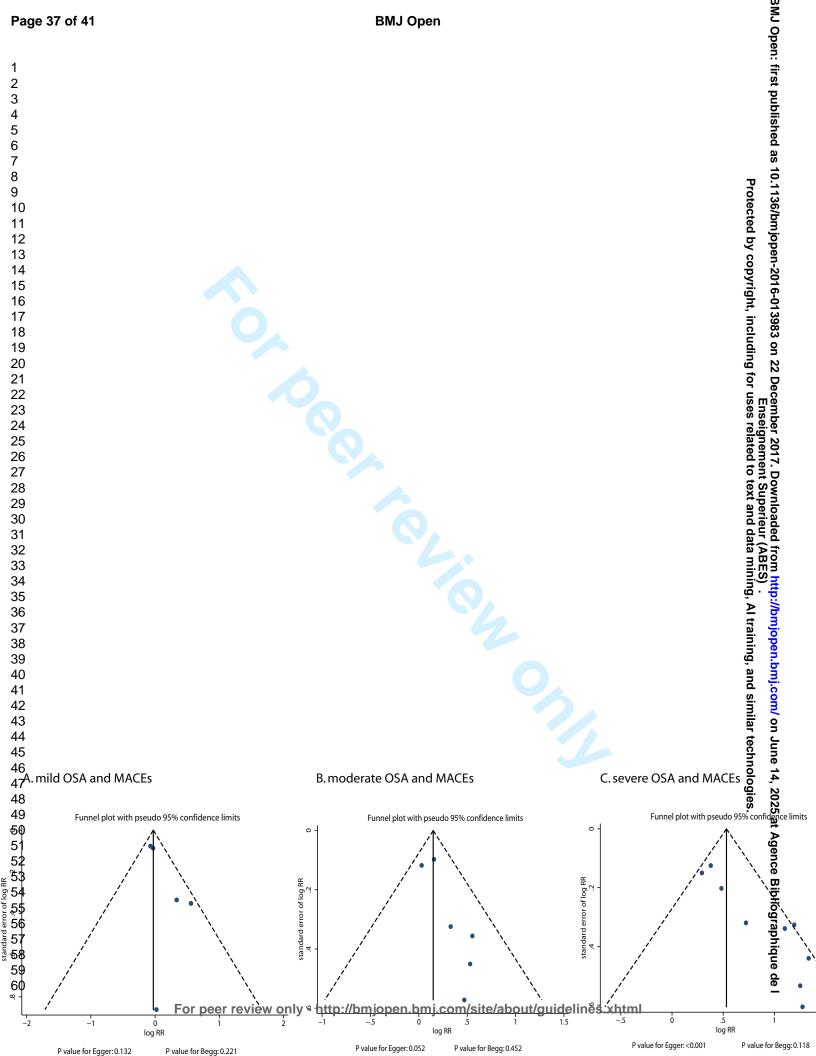
Figure 5. Funnel plots 











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	Heart Attack OR Heart Attacks OR Myocardial Infarct OR Infarct, Myocardial OR
	Infarcts, Myocardial OR Myocardial Infarcts
#15	"Angina Pectoris" [Mesh] OR "Angina, Stable" [Mesh] OR "Microvascular
	Angina" [Mesh] OR "Angina, Unstable" [Mesh] OR Stenocardia OR Stenocardias
	OR Angor Pectoris OR "angina" [All fields] OR "Coronary Artery Disease" [Mesh]
	OR "CAD" OR "ischemic heart disease" [All fields] OR "Heart Failure" [Mesh]
	OR "Heart Failure, Diastolic" [Mesh] OR "Heart Failure, Systolic" [Mesh]
#16	"Cerebrovascular Disorders" [Mesh] OR "cerebrovascular" [All fields] OR "stroke*"
#17	"Death" [Mesh] OR Determination of Death OR Near-Death Experience OR
	Cardiac Death OR Death, Cardiac OR "Mortality" [Mesh] OR "mortality" [All
	fields] OR "mortality*"
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	"Prospective Studies" [Mesh] OR "Cohort Studies" [Mesh] OR "Follow-Up
	Studies" [Mesh] OR "prospective study" OR "cohort study" OR "follow-up study"
#20	#9 AND #18 AND #19

7

#### Checklist for cohort, case-control, and cross-sectional studies (combined) Section/Topic Item # Recommendation Reported on page # Title and abstract (a) Indicate the study's design with a commonly used term in the title or the abstract 1 1 (b) Provide in the abstract an informative and balanced summary of what was done and what was found 2 Introduction 3 - 4Background/rationale 2 Explain the scientific background and rationale for the investigation being reported 3 Objectives 3 State specific objectives, including any pre-specified hypotheses 4 Methods 4-7 Study design 4 Present key elements of study design early in the paper 4 Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data Setting 5 collection Participants 6 (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic Variables 7 criteria, if applicable Data sources/ measurement 8\* For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe 4 comparability of assessment methods if there is more than one group 9 Describe any efforts to address potential sources of bias Bias Study size 10 Explain how the study size was arrived at Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen 5 - 6and why Statistical methods (a) Describe all statistical methods, including those used to control for confounding 12 6 (b) Describe any methods used to examine subgroups and interactions 6

## STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology\*

(c) Explain how missing data were addressed

(d) Cohort study—If applicable, explain how loss to follow-up was addressed

Case-control study—If applicable, explain how matching of cases and controls was addressed

Page	41	of 41	

**BMJ Open** 

	Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
	(e) Describe any sensitivity analyses	
Results		7-20
Participants	13* (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	
	confirmed eligible, included in the study, completing follow-up, and analysed	
	(b) Give reasons for non-participation at each stage	
	(c) Consider use of a flow diagram	
Descriptive data	14* (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and	
	potential confounders	
	(b) Indicate number of participants with missing data for each variable of interest	
	(c) Cohort study—Summarise follow-up time (eg, average and total amount)	
Outcome data	15* Cohort study—Report numbers of outcome events or summary measures over time	
	Case-control study—Report numbers in each exposure category, or summary measures of exposure	
	Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16 ( <i>a</i> ) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95%	
	confidence interval). Make clear which confounders were adjusted for and why they were included	
	(b) Report category boundaries when continuous variables were categorized	
	(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion		21-23
Key results	18 Summarise key results with reference to study objectives	22
Limitations	19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction	
	and magnitude of any potential bias	
Interpretation	20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results	
	from similar studies, and other relevant evidence	
Generalisability	21 Discuss the generalisability (external validity) of the study results	23
Other information		
Funding	22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies. Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# **BMJ Open**

## Association of obstructive sleep apnea with the risk of vascular outcomes and all-cause mortality: a meta-analysis

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<b>Primary Subject Heading</b> :	Neurology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	meta-analysis, mortality, obstructive sleep apnea, vascular outcome



#### **BMJ Open**

Association of obstructive sleep apnea with the risk of vascular outcomes and all-cause mortality: a meta-analysis

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Word count: 5459

#### Abstract

Objective: This study aimed to conduct a meta-analysis to explore and summarize the evidence regarding the association between obstructive sleep apnea (OSA) and the subsequent risk of vascular outcomes and all-cause mortality.

Methods: Electronic databases PubMed, Embase, and the Cochrane Library were searched to identify studies conducted through May 2016. Prospective cohort studies that reported effect estimates with 95% confidence intervals of major adverse cardiac events (MACEs), coronary heart disease (CHD), stroke, cardiac death, all-cause mortality, and heart failure for different levels versus the lowest level of OSA were included.

Results: A total of 16 cohort studies reporting data on 24,308 individuals were included. Of these, 11 studies reported healthy participants, and the remaining 5 studies reported participants with different diseases. Severe OSA was associated with a greater risk of MACEs (P < 0.001), CHD (P = 0.003), stroke (P < 0.001), cardiac death (P = 0.003), and all-cause mortality (P < 0.001); moderate OSA had a harmful impact on MACEs (P = 0.034) and CHD (P = 0.026); and no significant association was found between mild OSA and the risk of vascular outcomes or all-cause mortality (P > 0.05). Finally, no evidence of a factor-specific difference in the risk ratio for MACEs among participants with different levels of OSA compared with those with the lowest level of OSA was found.

Conclusions: Severe and moderate OSAs were associated with an increased risk of

#### BMJ Open

vascular outcomes and all-cause mortality. This relationship might differ between genders. Therefore, further large-scale prospective studies are needed to verify this difference.

Key words: Meta-analysis; mortality, obstructive sleep apnea, vascular outcome

#### **Article Summary:**

Strengths and limitations of this study:

1. The degree of association of OSA with fatal and nonfatal cardiovascular diseases (CVDs) was gender specific.

2. It provided statistical evidence on the association of moderate-to-severe OSA with MACEs.

3. The peculiar study design assessed risk ratios as per patient characteristics.

4. Quantitative data were used to emphasize the association of OSA as a poignant factor with CVDs.

#### Introduction

Obstructive sleep apnea (OSA) affects 24% of middle-aged men and 9% of women in the United States, but daytime sleepiness was reported in 17% and 22% of these

subjects, respectively [1]. OSA is an increasingly prevalent condition characterized by repetitive obstruction of the upper airway during sleep accompanied by episodic hypoxia, arousal, and sleep fragmentation [2]. Previous studies suggested that OSA was associated with an increased risk of glaucoma, diabetic kidney disease, and metabolic syndrome [3-5]. However, data on the association between OSA and the risk of subsequent vascular outcomes and mortality are both limited and inconclusive. Furthermore, whether these relationships differ according to the characteristics of patients with OSA also needs to be verified.

Several meta-analyses have illustrated that continuous positive airway pressure (CPAP) interventions aimed at OSA may reduce the risk of cardiovascular outcomes. Kim et al. [6] showed that CPAP treatment for OSA was associated with a lower incidence of stroke and cardiac events. Furthermore, Bratton et al. [7] indicated that use of both CPAP and mandibular advancement devices was associated with a reduction in the blood pressure among patients with OSA. Nadeem et al. [8] suggested that CPAP treatment for OSA seemed to improve dyslipidemia (decrease in total cholesterol and low-density lipoprotein, and increase in high-density lipoprotein), whereas it did not appear to affect the triglyceride levels. These studies demonstrated that patients with OSA who received interventions had a reduced risk of cardiovascular diseases. Therefore, clarifying the relationship between OSA and vascular outcomes is particularly important as it has not been definitively determined. This study attempted to perform a large-scale examination of the available prospective studies to determine the association of OSA with the potential risk of vascular

outcomes and all-cause mortality.

#### Methods

#### Data sources, search strategy, and selection criteria

This study was conducted and reported according to the Meta-analysis of Observational Studies in Epidemiology protocol [9].

Any prospective cohort study that examined the relationship between OSA and vascular outcomes or all-cause mortality was eligible for inclusion into this study, and no restrictions were placed on language or publication status (e.g., published, in press, or in progress). Electronic databases PubMed, Embase, and the Cochrane Library were searched for articles published through May 2016, using the terms "sleep apnea" OR "obstructive sleep apneas" AND ("cardiovascular disease" OR "stroke" OR "cardiac death" OR "mortality" OR "death" OR "CVD" OR "myocardial infarction" OR "coronary events") AND "clinical trials" AND "human" as the search terms (Supplemental 1). Manual searches of reference lists were also conducted from all the relevant original and reviewed articles to identify additional eligible studies. The medical subject heading, methods, patient population, design, exposure, and outcome variables of these articles were used to identify the relevant studies.

The literature search was independently undertaken by two authors using a standardized approach. Any inconsistencies between these two authors were settled by the primary author until a consensus was reached. The study was eligible for inclusion if the following criteria were met: (1) the study had a prospective cohort

design; (2) the study investigated the association between OSA and the risk of major adverse cardiac events (MACEs), coronary heart disease (CHD), stroke, cardiac death, all-cause mortality, and heart failure; and (3) the authors reported effect estimates [risk ratio (RR), hazard ratio (HR), or odds ratio (OR)] and 95% confidence intervals (CIs) for comparisons of different levels of OSA versus lowest OSA level. All case-control studies were excluded because various confounding factors could bias the results.

#### Data collection and quality assessment

The data collected included the first author's name, publication year, country, sample size, mean age at baseline, percentage of male patients, body mass index (BMI), disease status, assessment of OSA, follow-up duration, effect estimate and its 95% CI, reported endpoints, and covariates in the fully adjusted model. For studies that reported several multivariable adjusted RRs, the effect estimate that was maximally adjusted for potential confounders was selected.

The Newcastle–Ottawa Scale (NOS), which is quite comprehensive and has been partially validated for evaluating the quality of observational studies in the meta-analysis, was used to evaluate the methodological quality [10]. The NOS is based on the following three subscales: selection (4 items), comparability (1 item), and outcome (3 items). A "star system" (range, 0–9) was developed for assessment (Table 1). The data extraction and quality assessment were conducted independently by two authors. Information was examined and adjudicated independently by an

additional author referring to the original studies.

#### Statistical analysis

The relationship between OSA and the risk of vascular outcomes or all-cause mortality based on the effect estimate (OR, RR, or HR) and its 95% CI was examined in each study. HR was considered to be equivalent to RR in cohort studies. Given the low incidence of vascular outcomes and all-cause mortality, ORs could be considered as accurate estimates of RRs. A semi-parametric method was first used to evaluate the association between mild OSA [apnea-hypopnea index (AHI): 5-15], moderate OSA (AHI: 15-30), severe OSA (AHI > 30), and the risk of vascular outcomes or all-cause mortality to analyze the trend between OSA levels and vascular outcomes or all-cause mortality risk [11]. Each category of AHI levels was established based on its calculated median, and the control category was composed of participants with lowest AHI or normal participants in each study. Furthermore, when more than one median of AHI levels in each study was classified into one of these three categories, the fixed-effects model was used to calculate their summary RRs and 95% CIs for effect estimates of each category [12]. If the study data were not broken down by AHI, rather by ODI, each category of OSA was referred to the clinicians. The random-effects model was then used to calculate summary RRs and 95% CIs for mild, moderate, and severe OSA versus normal [13]. Finally, the relative RRs and the corresponding 95% CIs were estimated using specific RRs and 95% CIs after considering the country, mean age, gender, BMI, disease status, and duration of the follow-up period [14].

Heterogeneity between studies was investigated using the Q statistic, and P values <0.10 was considered as indicative of significant heterogeneity [15–16]. Subgroup analyses were conducted for mild, moderate, and severe OSA and the risk of MACEs based on the country, mean age, gender, BMI, disease status, and duration of the follow-up period. A sensitivity analysis was also performed by removing each individual study from the meta-analysis [17]. Several methods were used to check for potential publication bias. Visual inspections of funnel plots for MACEs were conducted. The Egger [18] and Begg [19] tests were also used to statistically assess publication bias for MACEs. All reported P values were two sided, and P values <0.05 were considered statistically significant for all included studies. Statistical analyses were performed using the STATA software (version 12.0; Stata Corporation, TX, USA).

#### Results

#### Literature search

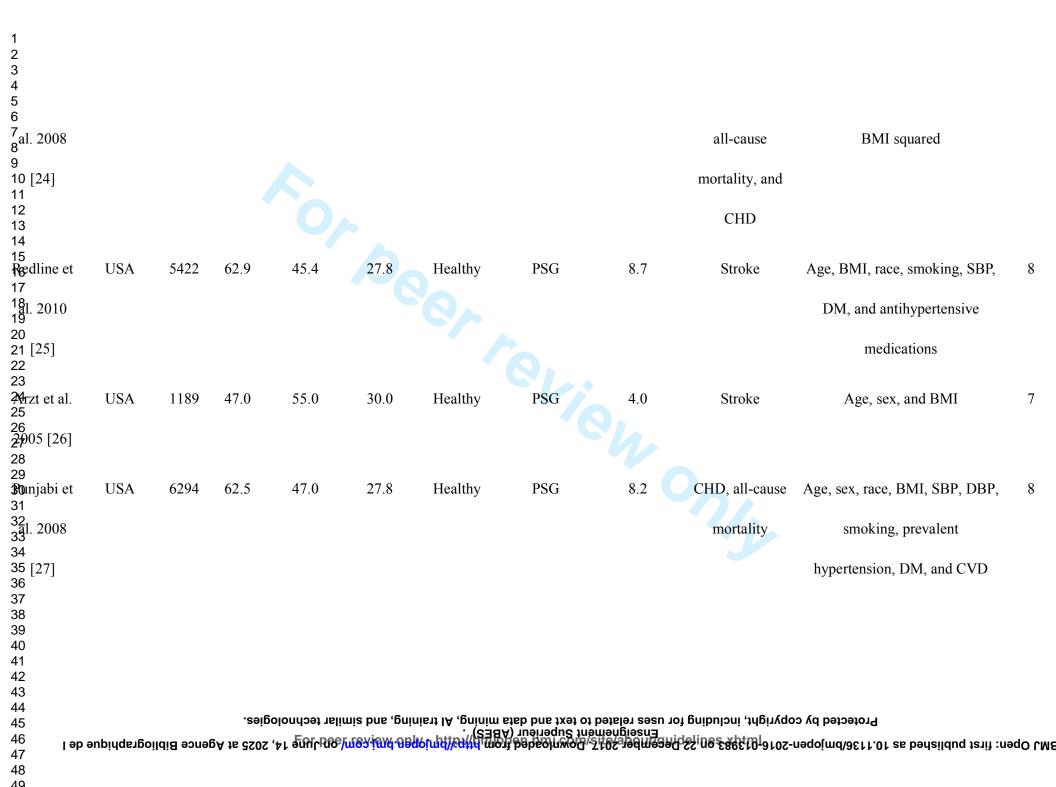
The results of the study-selection process are shown in Figure 1. An initial electronic search yielded 3282 articles, of which 3236 duplicates and irrelevant studies were excluded, and 46 potentially eligible studies were selected. After detailed evaluations, 16 prospective studies were selected for the final meta-analysis [20-35]. No new studies qualified for inclusion after a manual search of the reference lists of these studies. The general characteristics of the included studies are presented in Table 1.

A total of 16 studies with 24,308 individuals qualified for this study. The follow-up period for participants was 2.9-18.0 years, while 73-10,149 individuals were included in each study. Eight studies were conducted in the United States, four in Spain, one in Sweden, one in Portugal, one in Hungary, and one in Canada. Furthermore, 11 studies reported healthy participants, and the remaining 5 studies reported participants with different diseases. The mean BMI ranged from 26.8 to 34.0 kg/m<sup>2</sup>. Fourteen studies used polysomnography (PSG), and the remaining one study used limited PSG to assess the levels of OSA. The study quality was assessed using the NOS (Table 1). Overall, one study had a score of 9, six studies had a score of 8, seven studies had a score of 7, and the remaining two studies had a score of 6. . ha.

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3 4 5											
6 7			Tal	hla 1 Basalina	characteris	tic of studies	included in the	systematic revi	ew and meta-anal	ueie	
8 9			1 a		characteris		mended in the	systematic revi	ew and meta-anar	y 515	
10 11Study	Country	Sampl	Mean	Percentage	BMI	Disease	Assessment	Follow-up	Reported	Adjusted factors	NOS
12 13 14		e size	age	male (%)		status	OSA	duration	outcomes		score
15 16 17								(year)			
18 MPooe et a 20	ll. Sweden	408	59.1	58.4	27.0	CAD	Limited	5.1	CHD, stroke,	Age, sex, BMI, hypertension,	7
21 22000 [20	]						PSG		all-cause	DM, LVF, and coronary	
23 24 25 26									mortality	intervention	
27 Ciottlieb o	et USA	4422	62.4	43.5	28.2	Healthy	PSG	8.7	HF	Age, race, BMI, smoking, DM,	8
29 301. 2010 31										SBP, DBP, TC, HDL-C,	
32 33 [21] 34										lipid-lowering medications, and	
35 36										antihypertensive medications	
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Page 11 of 5	3					E	3MJ Open				
1 2 3 4 5 6 Zampos-R	c .	1117			266		NG	6.0			0
9	Spain	1116	56.1	0.0	36.6	Healthy	PSG	6.0	Cardiac death	Age, BMI, DM, hypertension,	8
d <b>@</b> riguez et 11 12 13 14 15 [22] 16 17										and previous CVD	
Marin et al.	Spain	1729	49.9	100	28.7	Healthy	PSG	10.1	Cardiac death	Age, diagnostic group, presence	9
20 21005 [23]									and CHD	of CVD, DM, hypertension, lipid	
22 23 24										disorders, smoking, alcohol, SBP	
22 23 24 25 26 27										DBP, blood glucose, TC, TG, and	
28 29										use of antihypertensive,	
30 31 32										lipid-lowering and antidiabetic	
31 32 33 34 35										drugs	
36 3Young et 38 39 40 41 42 43 44	USA	1522	48.0	55.0	28.6	Healthy	PSG	18.0		Age, age-squared, sex, BMI, and	8
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Page 13 of \$	53					В	MJ Open				
1 2 3 4 5 6											
Shah et al.	USA	1436	59.7	69.4	32.9	Healthy	PSG	2.9	CHD, cardiac	Age, race, sex, smoking, alcohol,	7
9 20010[28] 11 12 13 14									death	BMI, AF, DM, hypertension, and hyperlipidemia	
14 15 Y <b>g</b> ggi et al.	USA	1022	60.2	71.3	32.8	Healthy	PSG	3.4	Stroke and	Age, sex, race, smoking, alcohol,	8
17 19005 [29] 19									all-cause	BMI, DM, hyperlipidemia, AF,	
20 21 22 23									mortality	and hypertension	
23 Martı 'nez- 25	Spain	166	73.3	59.0	28.1	Ischemic	PSG	5.0	All-cause	Age, sex, Barthel index, AHI,	7
84 <sup>4</sup> artı'nez- 25 26 ≨ <del>y</del> arcı'a et						Stroke			mortality	and CPAP treatment groups,	
28 291. 2009 30 31 32 [30] 33 34 35										previous stroke or TIA, diabetes, hypercholesterolemia, BMI, smoking, arterial hypertension,	
36 37 38 39 40 41										atrial fibrillation, significant	
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1 2 3 4 5 6 7 8 9 10										carotid stenosis, and fibrinogen levels	
11 12 Munoz et	Spain	1034	79.8	57.0	26.8	Healthy	PSG	6.0	Stroke	Sex	7
12 14 15 16. 2006 17 18 [31] 19 20 21 20 21 22ão et al.	opun	1051	75.0				100		Suoke	JUK	,
21 12 ao et al.	Portugal	73	62.4	75.0	27.6	Acute	PSG	6.3	CHD	Sex	7
22 23 22016 [32] 25 26 27 28 29						coronary syndrome					
29 \$@rnadi et 31 32 33 31. 2014 33 34 35 [33] 36 37 20	Hungary	100	51.0	56.8	26.8	Kidney transplant	PSG	6.3	All-cause mortality	Unadjusted	6
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Page 15 of \$	53					Bl	BMJ Open							
1 2 3 4 5 6														
Kendzersk	Canada	10149	49.9	62.0	30.1	Healthy	PSG	5.7	All-cause	Traditional CV risk factors	7			
9 10a et al. 11 12 1314 [34] 14									mortality					
15 ₩son et al.	USA	281	65.0	98.0	34.0	Ischemic	PSG	4.1	All-cause	NA	6			
17 19 20 21 22 23 24 25 26 27 28						heart disease and myocardial injury		94	mortality					
29 30	AF, atrial	fibrillatio	n; BMI, 1	body mass in	dex; CAD,	, coronary arter	y disease; CH	D, coronary he	art disease; CPAP,	continuous positive airway				
31 32 33	pressure; (	CV, cardio	ovascular	; DBP, diasto	olic blood	pressure; DM,	diabetes melli	tus; HDL-C, h	igh-density lipopr	otein cholesterol; HF, heart				
34 35	failure; LVF, left ventricular function; OSA, obstructive sleep apnea; PSG, polysomnography; SBP, systolic blood pressure; TC, total cholesterol;													

TG, triglyceride; TIA, transient ischemic attack.

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#### **OSA** and MACE risk

Table 2. Summary of the relative risks of all outcomes evaluated

		E	MJ Open			Page 1		
OSA ai	nd MACE risk					Protected by copyright, including for uses related to text and da Pa		
The	summary RRs showe	d that mil	d OSA was not as	sociated w	ith MACEs (RR:			
0.98; 9	5% CI: 0.87–1.11; P	= 0.741;	Fig. 2 and Table 2	2). Further	more, the pooled	Protec		
analysis results for moderate and severe OSA indicated that they had a harmful effect								
on the	risk of MACEs (mode	rate: RR,	1.16; 95% CI, 1.01-	-1.33; <i>P</i> =	0.034; Fig. 3 and	copyri		
Table 2	2; severe: RR, 2.04; 9	95% CI, 1	1.56–2.66; $P < 0.0$	01; Fig. 4	and Table 2). A	ght, inc		
subgrou	up analysis for MACI	Es was co	nducted to minimize	ze heterog	eneity among the	sluding		
include	ed studies and evaluate	e the relat	tionship between O	SA and M	ACEs in specific	for us		
subpop	ulations (Table 3). O	verall, par	rticipants with mod	erate OSA	were associated	es relat		
with an	increased risk of MA	CEs if inc	lividuals did not ha	ve other di	seases (RR: 1.16;	ed to to		
95% C	I: 1.01–1.33; $P = 0.0$	34). Furtl	hermore, no signifi	cant assoc	iation was found	ext and		
betwee	n severe OSA and MA	ACEs if th	ne study included o	nly wome	n (RR: 1.98; 95%	data m		
CI: 0.6	64-6.06; P = 0.234);	in other	subsets, severe OS	SA was as	sociated with an	ining		
increas	ed risk of MACEs	(Table 3	). Finally, no evi	dence of	a factor-specific	Al train		
differer	nce was found in the l	RR for M	ACEs among partic	cipants wit	h OSA compared	iing, an		
with co	ontrols (Table 3).					ld simil		
	Table 2. Summary	of the rel	ative risks of all ou	tcomes eva	luated	, Al training, and similar technologies		
itcomes	Mild OSA	<i>P</i> value	Moderate OSA	P value	Severe OSA	<i>P</i> value S		
IACEs	0.98 (0.87–1.11)	0.741	1.16 (1.01–1.33)	0.034	2.04 (1.56–2.66)	<0.001		
CHD	1.25 (0.95–1.66)	0.117	1.38 (1.04–1.83)	0.026	1.63 (1.18–2.26)	0.003		

	Stroke	1.29	(0.69–2.41)	0.4	24 1.35	(0.82–2.23)	0.2	45 2.15	5 (1.4	2-3.24)	) <(	0.00	
Car	Cardiac death		(0.68–4.76)	0.2	36 1.11	(0.53–2.35)	0.7	81 2.96	6 (1.4	5-6.01)	) 0	.003	
All-ca	use mortality	1.26 (0.77–2.07)		0.354 1.04		4 (0.60–1.79) 0.8		95 1.54	4 (1.21–1.97)		) <(	< 0.00	
Не	eart failure	1.02 (0.78–1.34)		0.868 1.07		7 (0.74–1.54) 0.7		19 1.44	4 (0.94–2.21)		) 0	0.097	
	CHD, Cor sleep apne			-		r cardiovascul alyses for MA		vent; OSA	, obst	tructive			
Variable	Subgroup		Mild OSA		P value	Moderate OS	A	<i>P</i> value	Sev	vere OS	A	Р	
Country	USA		1.00 (0.85–1	.17)	0.977	1.14 (0.99–1.	32)	0.064	1.9	0 (1.35-	-2.67)	<	
	Other		1.02 (0.19–5	.52)	0.982	1.44 (0.83–2.	50)	0.198	2.3	5 (1.52-	-3.65)	<	
	USA vs other		0.98 (0.18–5	.32)	0.982	0.79 (0.45–1	40)	0.422	0.8	1 (0.46-	-1.41)	0.	
Mean age	≥60		0.96 (0.86–1	.08)	0.540	1.13 (0.97–1.	33)	0.117	1.7	8 (1.23-	-2.57)		
	<60		1.40 (0.73–2.	.70)	0.315	1.51 (0.94–2.4	41)	0.086	2.3	1 (1.64-	-3.24)	<	
	≥60 vs <60		0.69 (0.35–1.	.33)	0.265	0.75 (0.46–1.2	23)	0.252	0.7	7 (0.47-	-1.27)	0. <b>0.</b>	
Gender	Male		0.92 (0.73–1.	.15)	0.455	1.10 (0.85–1.4	42)	0.449	1.8	1 (1.14-	-2.89)	0.	
	Female		1.97 (0.47–8	.25)	0.353	1.36 (0.67–2.	76)	0.399	1.9	8 (0.64-	-6.06)	0.	
	Male	vs	0.47 (0.11–1.	.99)	0.304	0.81 (0.38–1.	72)	0.581	0.9	1 (0.27-	-3.08)	0.	
	female												

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4 5	BMI	≥30	1.75 (0.88–3.49)	0.111	1.70 (0.94–3.07)	0.079	2.72 (1.80-4.10)	<0.001 blished
6 7 8		<30	0.96 (0.86–1.07)	0.449	1.14 (0.99–1.31)	0.078	1.80 (1.36–2.38)	<0.001 s
9 10 11		≥30 vs <30	1.82 (0.91–3.66)	0.092	1.49 (0.81–2.74)	0.198	1.51 (0.92–2.49)	1136/bmj 0.10 <b>tec</b> ted
12 13 14	Disease	Healthy	1.00 (0.85–1.17)	0.977	1.16 (1.01–1.33)	0.034	2.12 (1.53–2.94)	open-20 by 91 <0.00py
15 16 17 18	statues	Other	1.02 (0.19–5.52)	0.982	-	-	1.96 (1.01–3.81)	0.1136/bmjopen-2016-013983 on 22 December Protected by 90 pyright including for uses re 0.830 0.
19 20		Healthy vs	0.98 (0.18–5.32)	0.982	_	-	1.08 (0.52–2.27)	<b>3 on 22</b>
21 22 23 24		Other						Decembe Ense for uses r
25 26	Follow-up	≥6	0.96 (0.86–1.07)	0.449	1.14 (0.99–1.31)	0.064	2.06 (1.43–2.95)	<0.0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
27 28 29	duration	<6	1.75 (0.88–3.49)	0.111	1.74 (0.87–3.49)	0.120	2.10 (1.39–3.17)	Downloaded nt Superieur o test and da
30 31 32 33		≥6 vs <6	0.55 (0.27–1.10)	0.092	0.66 (0.32–1.33)	0.242	0.98 (0.57–1.70)	aded from nd data mi
34								<u>د ی</u>

OSA, obstructive sleep apnea.

#### **OSA** and CHD risk

The pooled data of meta-analysis showed that mild OSA was not associated with the risk of CHD (RR: 1.25; 95% CI: 0.95–1.66; P = 0.117; Table 2 and Supplemental 2), whereas moderate OSA (RR: 1.38; 95% CI: 1.04–1.83; P = 0.026; Table 2 and Supplemental 2) and severe OSA (RR: 1.63; 95% CI: 1.18–2.26; P = 0.003; Table 2 and Supplemental 2) were associated with a significantly increased risk of CHD. Stratified analyses according to gender were conducted for different levels of OSA versus normal group, and it was found that patients with severe OSA had significantly

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19 of 53			BMJ	Open			
	increased the	risk of CHD in mer	n (RR: 1.6	5; 95% CI: 1.06–2.5	57; $P = 0.02$	27). No other	
	significant di	fferences were detec	eted (Table	e 4).			
		Table 4. Ge	nder diffe	rence for other outc	omes		Protect
Outcome	Subgroup	Mild OSA	<i>P</i> value	Moderate OSA	P value	Severe OSA	ed by co
							Protected by copyright,
CHD	Men	0.93 (0.72–1.21)	0.596	1.09 (0.80–1.48)	0.582	1.65 (1.06–2.57)	, inceaning
	Women	1.92 (0.43-8.64)	0.394	1.51 (0.38–5.97)	0.559	1.10 (0.12–9.87)	g royuses
	Men vs women	0.48 (0.11–2.22)	0.351	0.72 (0.18–2.96)	0.651	1.50 (0.16–14.22)	0. 0.
Stroke	Men	1.86 (0.67–5.14)	0.232	1.86 (0.70-4.95)	0.214	2.86 (1.10-7.41)	0.00 0.00
	Women	1.34 (0.76–2.36)	0.311	1.20 (0.67–2.15)	0.542	1.21 (0.65–2.25)	ano Qajia 0.
	Men vs women	1.39 (0.43–4.45)	0.581	1.55 (0.50–4.84)	0.451	2.36 (0.76–7.38)	ta mintag, 0.
Cardiac	Men	_	_	1.15 (0.41–3.23)	0.791	2.87 (1.13–7.27)	Al tranı 0.01
death	Women	_	_	0.94 (0.19–4.61)	0.939	3.71 (0.41–33.87)	าg, aคส 0.4 ร
	Men vs women	_	_	1.22 (0.18-8.17)	0.935	0.77 (0.07–8.49)	0. atta similatorechnotegiles
All-cause	Men	_	_	_	-	1.72 (1.22–2.43)	0.00
mortality	Women	_	_	_	_	3.50 (1.23–9.97)	es. 0.0
	Men vs women	_	_	_	_	0.49 (0.16–1.48)	0.2
Heart	Men	0.88 (0.57–1.35)	0.561	1.13 (0.68–1.88)	0.639	1.58 (0.93–2.67)	<b>9</b> , Al træning, afta similagrechno <b>e</b> gies. 0.0 0.2 0.0 0.0

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3 4	failure	Women	1.13 (0.80–1.60)	0.493	1.01 (0.60–1.70)	0.970	1.19 (0.56–2.52)	
5 6 7 8		Men vs women	0.78 (0.45–1.35)	0.376	1.12 (0.54–2.32)	0.762	1.33 (0.53–3.33)	
9 <sup>-</sup> 10 11		CHD, corona	ry heart disease; OS	A, obstru	ctive sleep apnea.			
12 13 14		OSA and stre	oke risk					
15 16 17		Pooled ana	lysis results indicate	ed no asso	ociation between mil	d OSA (RI	R: 1.29; 95%	
18 19 20		CI: 0.69–2.41	; $P = 0.424$ ; Table 2	2 and Sup	plemental 2) and mo	oderate OSA	A (RR: 1.35;	
21 22		95% CI: 0.8	2-2.23; P = 0.245;	Table 2	and Supplemental 2	2) and stro	ke, whereas	
23 24 25		severe OSA	was associated wit	h an inc	reased risk of strok	e (RR: 2.1	5; 95% CI:	
26 27 28		1.42–3.24; $P < 0.001$ ; Table 2 and Supplemental 2). Subgroup analysis on the basis of						
29 30		gender indicated that severe OSA had a harmful effect on the risk of stroke in men						
31 32 33		(RR: 2.86; 95	% CI: 1.10–7.41; <i>P</i>	= 0.031;	Table 4).			
34 35 36		OSA and car	diac death risk					
37 38 39		The summ	ary RRs showed th	nat mild	OSA (RR: 1.80; 95	% CI: 0.6	8–4.76; <i>P</i> =	
40 41		0.236; Table	2 and Supplemental	2) and m	oderate OSA (RR: 1	.11; 95% C	T: 0.53–2.35;	
42 43 44		P = 0.781; T	able 2 and Supplem	ental 2)	were not associated v	with cardia	c death risk,	
45 46		whereas seve	re OSA significantly	y increase	ed the risk of cardiac	c death (RF	R: 2.96; 95%	
47 48 49		CI: 1.45–6.0	1; $P = 0.003$ ; Table	2 and S	upplemental 2). Sub	group anal	ysis showed	
50 51 52		that severe C	SA was associated	with an i	ncreased risk of care	liac death	in men (RR:	
53 54		2.87; 95% CI	: 1.13 - 7.27; P = 0.0	26; Table	24).			
55 56 57 58		OSA and all-	cause mortality risk	Ţ				
59 60								

No significant association was found between mild OSA (RR: 1.26; 95% CI: 0.77–2.07; P = 0.354; Table 2 and Supplemental 2), moderate OSA (RR: 1.04; 95% CI: 0.60–1.79; P = 0.895; Table 2 and Supplemental 2), and all-cause mortality risk. However, severe OSA had a harmful impact on the all-cause mortality (RR: 1.54; 95% CI: 1.21–1.97; P < 0.001; Table 2 and Supplemental 2). Stratified analysis suggested that severe OSA increased the risk of all-cause mortality in men (RR: 1.72; 95% CI: 1.22–2.43; P = 0.002) and women (RR: 3.50; 95% CI: 1.23–9.97; P = 0.019; Table 4).

#### OSA and heart failure risk

The summary results indicated no significant differences between mild OSA (RR: 1.02; 95% CI: 0.78–1.34; P = 0.868), moderate OSA (RR: 1.07; 95% CI: 0.74–1.54; P = 0.719), and severe OSA (RR: 1.44; 95% CI: 0.94–2.21; P = 0.097), and the risk of heart failure (Table 2 and Supplemental 2). Subgroup analysis reported similar results compared with the overall analysis (Table 4).

#### **Publication bias**

Review of the funnel plots could not rule out the potential publication bias for MACEs (Fig. 5). The Egger and Begg test results showed no evidence of publication bias for MACEs of mild OSA (*P* value for Egger: 0.132; *P* value for Begg: 0.221) and moderate OSA (*P* value for Egger: 0.052; *P* value for Begg: 0.452). Although the Begg test showed no evidence of publication bias for MACEs of severe OSA (*P* = 0.118), the Egger test showed potential evidence of publication bias for MACEs of

severe OSA (P < 0.001). The conclusion did not change after adjustment for publication bias using the trim-and-fill method [36].

#### Discussion

The present study was based on prospective cohort studies and explored all possible correlations between OSA and the outcomes of MACEs, CHD, stroke, cardiac death, all-cause mortality, and heart failure. This large quantitative study included 24,308 individuals from 16 prospective cohort studies with a broad range of populations. The findings from the present meta-analysis suggested that mild OSA had no significant impact on the risk of vascular outcomes and all-cause mortality, moderate OSA was associated with an increased risk of MACEs and CHD, and severe OSA had a harmful effect on the risk of MACEs, CHD, stroke, cardiac death, and all-cause mortality.

A previous meta-analysis suggested that OSA was associated with stroke, but its relationship with ischemic heart disease and cardiovascular mortality needs further research [37]. However, this study could not illustrate the impact of different levels of OSA on the risk of serious cardiovascular outcomes. Further, Dong et al. suggested that moderate-to-severe OSA significantly increased the risk of cardiovascular diseases, in particular, the risk of stroke [38]. Similarly, Ge et al. indicated that severe OSA is a strong independent predictor of cardiovascular and all-cause mortality. CPAP treatment was associated with decreased cardiovascular mortality [39]. However, these two studies could not evaluate the association of OSA with the risk of vascular outcomes and all-cause mortality in specific subpopulations. In addition,

Wang et al. suggested that severe OSA significantly increased the risk of CHD and stroke, and all-cause mortality. A positive association with CHD was observed for moderate OSA but not for mild OSA [40]. However, whether this relationship differs according to the characteristics of participants remains unclear. Finally, Xie et al. conducted a meta-analysis to evaluate the relationship between OSA and recurrent vascular events and all-cause mortality [41]. However, they just compared the highest AHI versus lowest AHI, whereas the degree of OSA and subsequent adverse outcomes were not available. Therefore, a comprehensive meta-analysis of these prospective cohort studies was performed to evaluate any possible correlates between OSA and vascular outcomes. 3MJ Open: first published as 10.1136/bmjopen-2016-013983 on 22 December 2017. Downloaded from http://bmjopen.bmj.com/ on June 14, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

No significant difference was observed between mild OSA and the risk of vascular outcomes. However, several studies included in this study reported inconsistent results. Young et al. suggested that mild OSA significantly increased the risk of CHD by 92% [24], whereas Punjabi et al. indicated that mild OSA might have a harmful effect on the risk of CHD [27]. This might be because these two studies used healthy individuals as controls, which may make them more susceptible to acquired significant conclusion. Furthermore, most of these studies did not take into account potential confounders for the risk of cardiovascular disease. Moderate-to-severe OSA might play an important role in the risk of vascular outcomes. Shah et al. concluded that OSA increased the risk of coronary events or death from cardiovascular causes [28]. Nearly all included studies reported adverse outcomes for severe OSA. Previous studies indicated that OSA was a cause of diabetes, which was an independent risk

factor for MACEs. Multiple adjusted models might be biased as the adjusted variables are different, reflecting either mediation or confounding.

Subgroup analyses reported similar conclusions. Gender might have an impact on the relationship between OSA and CHD, stroke, or cardiac death, although the sex difference was not statistically significant. The possible reasons could be the lower prevalence of severe OSA in women and the later age of onset of OSA in women than in men. Furthermore, OSA in women always occurred after menopause. Physiological response to OSA is another reason for this nonsignificant difference. Finally, these conclusions might be unreliable because smaller cohorts were included in each subset. Therefore, further large-scale studies were needed to verify this difference. Therefore, a relative result was given, and a synthetic and comprehensive review was provided.

No significant difference was found between mild or moderate OSA and all-cause mortality, while severe OSA was associated with an increased risk of all-cause mortality. Further, these significant associations were also observed in men and women separately. Although the effect estimate in women was larger than that in men, no gender difference was found in the relationship between OSA and all-cause mortality. This might be because the number of studies that reported the relationship between severe OSA and all-cause mortality was smaller than expected, and a broad 95% CI was acquired. Therefore, the association of severe OSA with all-cause mortality in women was variable and should be verified in future large-scale prospective studies.

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Three strengths of this study should be highlighted. First, only prospective studies were included, which eliminated selection and recall bias, and could be of concern in retrospective case–control studies. Second, the large sample size allowed us to quantitatively assess the association of OSA with the risk of vascular outcomes and mortality, and thus the findings were potentially more robust than those of any individual study. Third, the summary RRs were calculated to evaluate any potential difference between subsets according to the characteristics of participants.

The limitations of this study were as follows: (1) the adjusted models were different across the included studies, and these factors might have played an important role in developing vascular outcomes; (2) in a meta-analysis of published studies, publication bias was an inevitable problem; and (3) the analysis used pooled data (individual data were not available), which restricted performing a more detailed relevant analysis and obtaining more comprehensive results.

The results of this study suggested that moderate-to-severe OSA might play an important role in the risk of vascular outcomes, especially for men. Future studies should focus on specific populations to analyze the gender difference to study the association between OSA and vascular outcomes.

#### **Author Contributions**

Chengjuan Xie carried out the studies, participated in collecting data, and drafted the manuscript. Ruolin Zhu performed the statistical analysis and participated in its design. Yanghua Tian and Kai Wang helped to draft the manuscript. All authors read

and approved the final manuscript.

Conflict of interests: All authors declare no conflict of interest.

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Data sharing statement: No additional data available.

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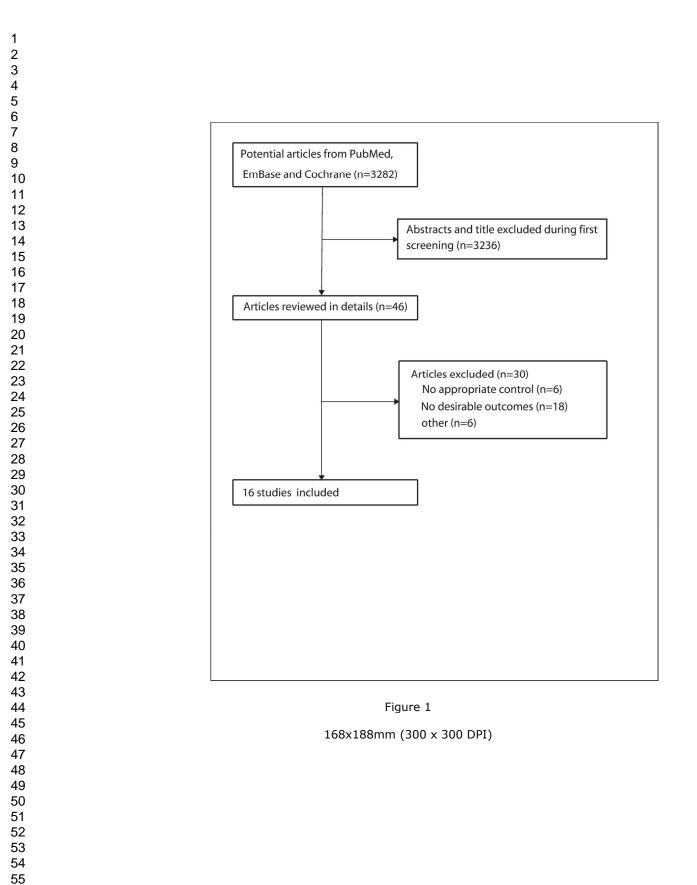
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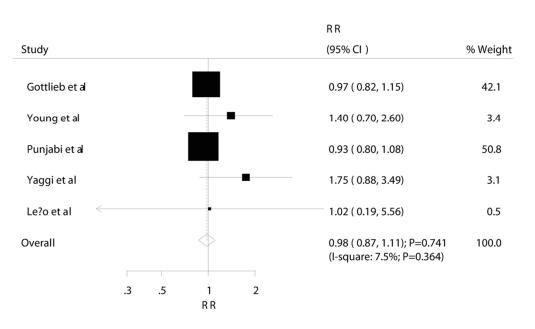
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cardiovascular disease and all-cause mortality: a meta-analysis of prospective
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in patients with cardiovascular or cerebrovascular disease: a
PRISMA-compliant systematic review and meta-analysis. Medicine
(Baltimore) 2014;93(29):e336. doi: 10.1097/MD.00000000000336.

### **Figure legends:**

- Figure 1. Study-selection process.
- Figure 2. Association between mild OSA and MACEs.
- Figure 3. Association between moderate OSA and MACEs.
- Figure 4. Association between severe OSA and MACEs.

Figure 5. Funnel plots.

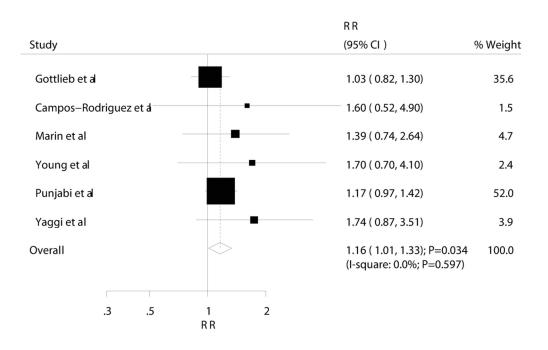






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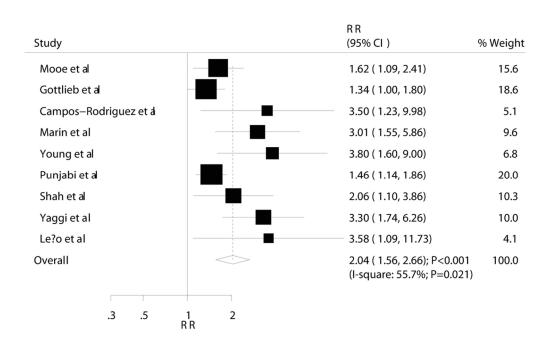
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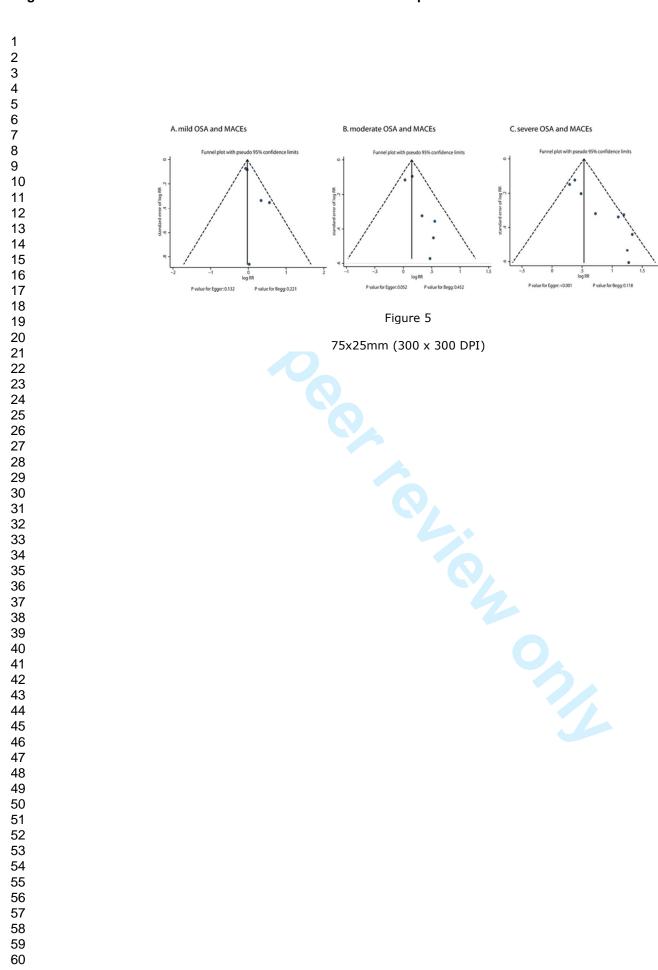
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Title:	
	Search strategy
#1	"Sleep Apnea, Obstructive" [Mesh] OR "OSA" [All fields] OR "OHS" [All fields]
#2	Apneas, Obstructive Sleep OR Obstructive Sleep Apneas OR Sleep Apneas, Obstructive OR Obstructive Sleep Apnea Syndrome OR Obstructive Sleep Apnea OR OSAHS OR Syndrome, Sleep Apnea, Obstructive OR Sleep Apnea Syndrome, Obstructive OR Apnea, Obstructive Sleep OR Sleep Apnea Hypopnea Syndrome OR Syndrome, Obstructive Sleep Apnea OR Upper Airway Resistance Sleep Apnea Syndrome OR Syndrome, Upper Airway Resistance, Sleep Apnea OR Hypoventilation Syndrome, Obesity OR Syndrome, Obesity Hypoventilation OR Pickwickian Syndrome OR Syndrome, Pickwickian OR Obesity-Hypoventilation Syndrome
#3	"Sleep Apnea Syndromes" [Mesh] OR "SAS" [All fields]
#4	Apnea Syndrome, Sleep OR Apnea Syndromes, Sleep OR Sleep Apnea Syndrome OR Apnea, Sleep OR Apneas, Sleep OR Sleep Apnea OR Sleep Apneas OR Sleep Hypopnea OR Hypopnea, Sleep OR Hypopneas, Sleep OR Sleep Hypopneas OR Sleep-Disordered Breathing OR Breathing, Sleep-Disordered OR Sleep Disordered Breathing OR Sleep Apnea, Mixed Central and Obstructive OR Mixed Central and Obstructive Sleep Apnea OR Sleep Apnea, Mixed OR Mixed Sleep Apnea OR Mixed Sleep Apneas OR Sleep Apneas, Mixed OR Hypersomnia with Periodic Respiration
#5	"Sleep Apnea, Central" [Mesh] OR "CSA" [All fields]
#6	Apneas, Central Sleep OR Central Sleep Apneas OR Sleep Apneas, Central OR Apnea, Central OR Apneas, Central OR Central Apnea OR Central Apneas OR Apnea, Central Sleep OR Apnea, Sleep, Central OR Sleep Apnea, Lethal Central OR Central Sleep Apnea OR Central Sleep Apnea Syndrome OR Central Sleep Disordered Breathing OR Hypoventilation, Central Alveolar OR Alveolar Hypoventilation, Central OR Alveolar Hypoventilations, Central OR Central Alveolar OR OR OR Hypoventilations, Central OR Central Sleep-Disordered OR Sleep-Disordered Breathing, Central Sleep-Disordered OR Breathings, Central Sleep-Disordered OR Central Sleep-Disordered Breathing OR Central Sleep-Disordered OR Central Sleep-Disordered Breathing OR Central Sleep-Disordered Breathings, Central Sleep-Disordered Breathing OR Sleep-Disordered Breathings, Central Sleep-Disordered Breathing OR Central Sleep-Disordered Breathings, Central OR Central Alveolar Hypoventilation Syndrome OR Central Sleep Disordered Breathing, Central OR Sleep-Disordered Breathings, Central OR Central Alveolar Hypoventilation Syndrome OR Central Sleep Apnea, Secondary OR Secondary Central Sleep Apnea OR Sleep Apnea, Newborn, Primary OR Primary Sleep Apneas of Newborn OR Newborn Primary Sleep Apneas OR Central Sleep Apnea, Primary OR Primary Central Sleep Apnea
#7	"Continuous Positive Airway Pressure" [Mesh] OR "CPAP" [All fields] OR "Continuous Positive Airway Pressure/therapy" [Mesh]
#8	CPAP Ventilation OR Ventilation, CPAP OR Biphasic Continuous Positive Airway Pressure OR Bilevel Continuous Positive Airway Pressure OR Nasal Continuous Positive Airway Pressure OR nCPAP Ventilation OR Ventilation, nCPAP OR Airway Pressure Release Ventilation OR APRV Ventilation Mode OR APRV Ventilation Modes OR Ventilation Mode, APRV OR Ventilation Modes, APRV

<b>#9</b>	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	"Cardiovascular System" [Mesh]
#11	"Death" [Mesh] OR Determination of Death OR Near-Death Experience OR
	Cardiac Death OR Death, Cardiac OR "Mortality" [Mesh] OR "mortality" [All
	fields] OR "Disease" [Mesh] OR "disease*"
#12	#10 AND #11
#13	"Cardiovascular Diseases" [Mesh] OR "CVD" OR Cardiovascular Disease OR
	Disease, Cardiovascular OR Diseases, Cardiovascular
#14	"Myocardial Infarction" [Mesh] OR "MI" OR Infarction, Myocardial OR
	Infarctions, Myocardial OR Myocardial Infarctions OR Cardiovascular Stroke OR
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	Heart Attack OR Heart Attacks OR Myocardial Infarct OR Infarct, Myocardial OR
	Infarcts, Myocardial OR Myocardial Infarcts
#15	"Angina Pectoris" [Mesh] OR "Angina, Stable" [Mesh] OR "Microvascular
	Angina" [Mesh] OR "Angina, Unstable" [Mesh] OR Stenocardia OR Stenocardias
	OR Angor Pectoris OR "angina" [All fields] OR "Coronary Artery Disease" [Mesh]
	OR "CAD" OR "ischemic heart disease" [All fields] OR "Heart Failure" [Mesh]
	OR "Heart Failure, Diastolic" [Mesh] OR "Heart Failure, Systolic" [Mesh]
#16	"Cerebrovascular Disorders" [Mesh] OR "cerebrovascular" [All fields] OR
	"stroke*"
#17	"Death" [Mesh] OR Determination of Death OR Near-Death Experience OR
	Cardiac Death OR Death, Cardiac OR "Mortality" [Mesh] OR "mortality" [All
	fields] OR "mortality*"
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	"Prospective Studies" [Mesh] OR "Cohort Studies" [Mesh] OR "Follow-Up
	Studies" [Mesh] OR "prospective study" OR "cohort study" OR "follow-up study"
#20	#9 AND #18 AND #19

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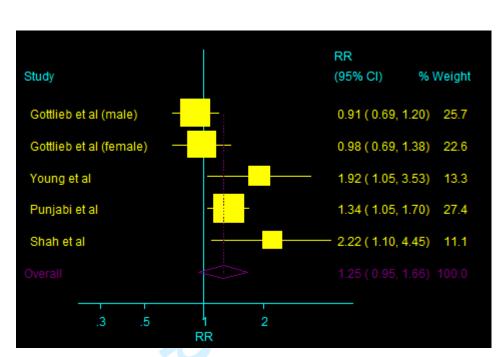


Figure S1. Association between mild OSA and CHD.

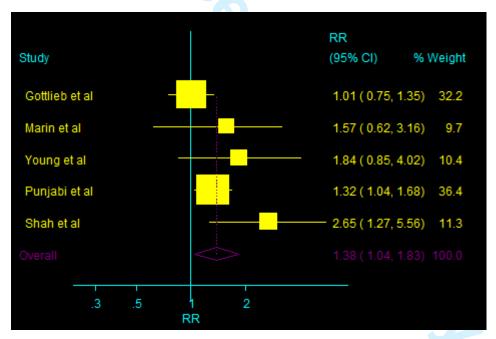


Figure S2. Association between moderate OSA and CHD.

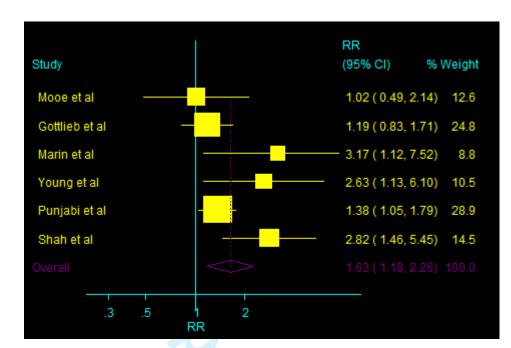
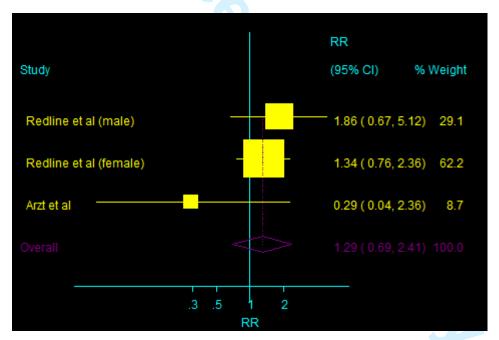
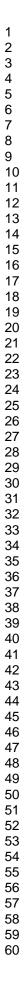


Figure S3. Association between severe OSA and CHD.



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Figure S4. Association between mild OSA and stroke.



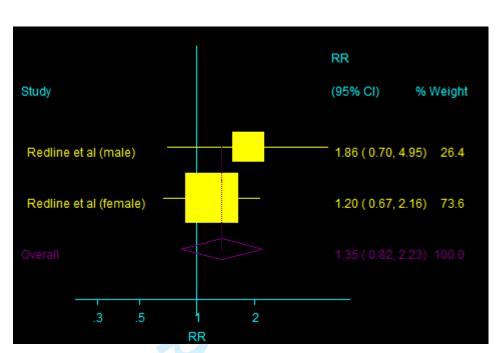


Figure S5. Association between moderate OSA and stroke.

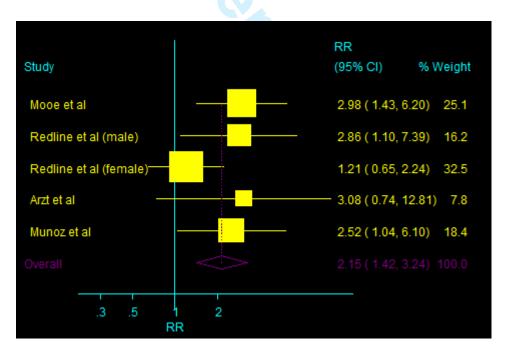


Figure S6. Association between severe OSA and stroke

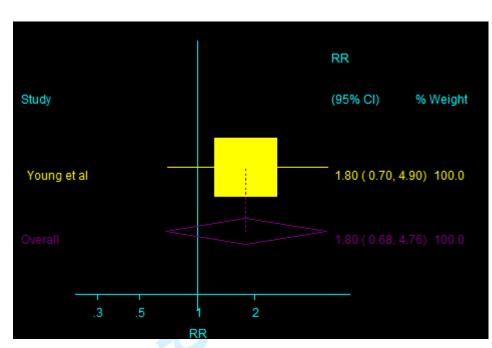
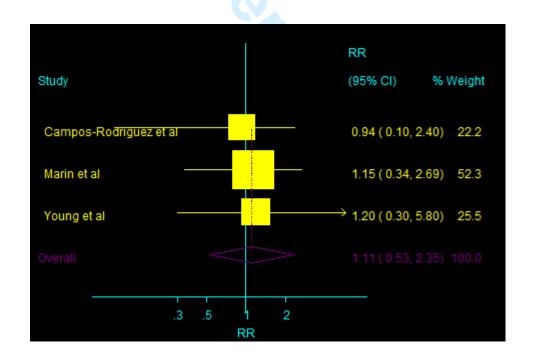
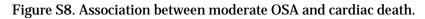
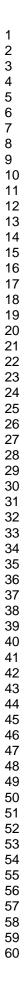


Figure S7. Association between mild OSA and cardiac death.







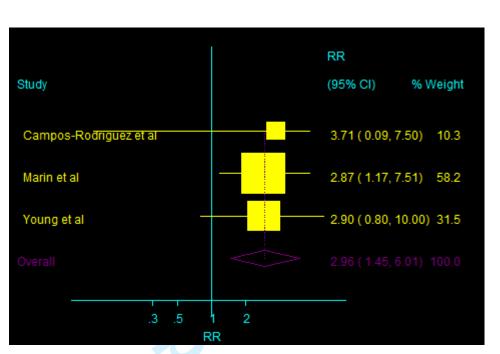


Figure S9. Association between severe OSA and cardiac death.

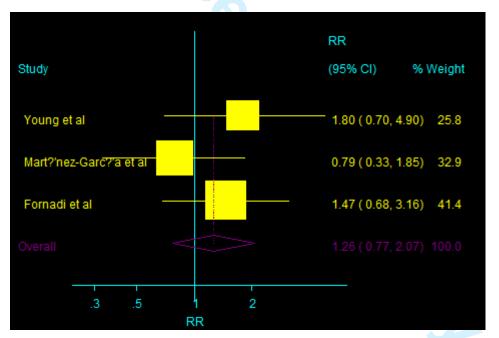


Figure S10. Association between mild OSA and all-cause death.

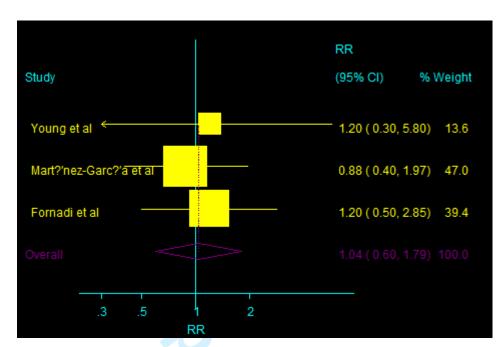


Figure S11. Association between moderate OSA and all-cause death.

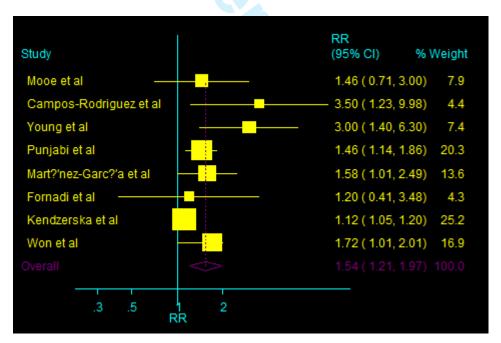
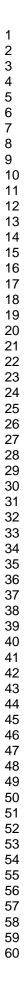


Figure S12. Association between severe OSA and all-cause death.

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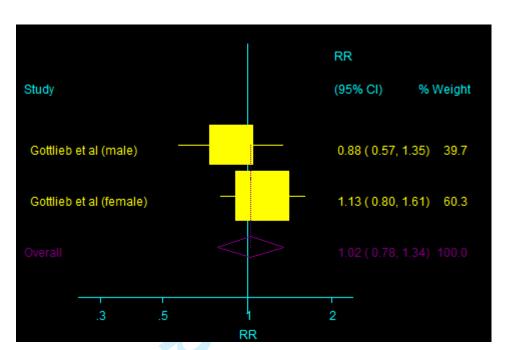


Figure S13. Association between mild OSA and heart failure.

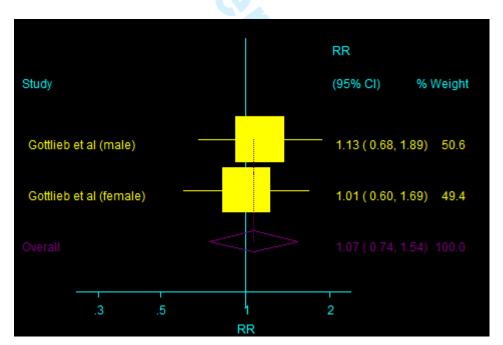


Figure S14. Association between moderate OSA and heart failure.

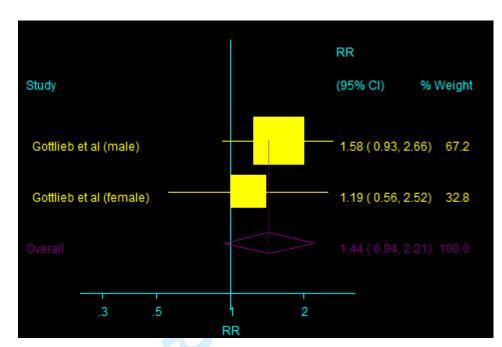


Figure S15. Association between severe OSA and heart failure.

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Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			3-4
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			4-7
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	<ul> <li>(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</li> <li>Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</li> <li>Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants</li> </ul>	
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	7
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed	7

## STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology\*

Page 51	l of 53
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**BMJ Open** 

	Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy					
	(e) Describe any sensitivity analyses					
Results						
Participants	13* (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed					
	(b) Give reasons for non-participation at each stage					
	(c) Consider use of a flow diagram					
Descriptive data	14* (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders					
	(b) Indicate number of participants with missing data for each variable of interest					
	(c) Cohort study—Summarise follow-up time (eg, average and total amount)					
Outcome data	15* Cohort study—Report numbers of outcome events or summary measures over time					
	Case-control study—Report numbers in each exposure category, or summary measures of exposure					
	Cross-sectional study—Report numbers of outcome events or summary measures					
Main results	16 ( <i>a</i> ) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included					
	(b) Report category boundaries when continuous variables were categorized					
	(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period					
Other analyses	17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses					
Discussion		21-23				
Key results	18 Summarise key results with reference to study objectives	22				
Limitations	19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias					
Interpretation	20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence					
Generalisability	21 Discuss the generalisability (external validity) of the study results	23				
Other information						
Funding	22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24				

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies. Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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## MOOSE Statement: Reporting Checklist for Authors, Editors, and Reviewers of Metaanalyses of Observational Studies

Reporting Criteria	Reported (Yes/No)	Reported on Page
Reporting of background should include	(	
Problem definition	Yes	3
Hypothesis statement	Yes	3
Description of study outcomes	Yes	3
Type of exposure or intervention used	Yes	3 - 4
Type of study designs used	Yes	4
Study population	Yes	4
Reporting of search strategy should include		
Qualifications of searchers (e.g., librarians and investigators)	Yes	4 - 5
Search strategy, including time period used in the synthesis and key words	Yes	5
Effort to include all available studies, including contact with authors	Yes	5
Databases and registries searched	Yes	4–5
Search software used, name and version, including special features used (e.g., explosion)	Yes	4-5
Use of hand searching (e.g., reference lists of obtained articles)	Yes	5
List of citations located and those excluded, including justification	Yes	8
Method of addressing articles published in languages other than English	Yes	4
Method of handling abstracts and unpublished studies	Yes	4–5
Description of any contact with authors	No	NA
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	No	5
Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	Yes	5-6
Documentation of how data were classified and coded (e.g., multiple raters, blinding and inter-rater reliability)	Yes	5-6
Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	Yes	6
Assessment of study quality, including blinding of quality assessors, and stratification or regression on possible predictors of study results	Yes	6

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Assessment of heterogeneity	Yes	7
Description of statistical methods (e.g., complete description of fixed-	Yes	6–7
or random-effects models, justification of whether the chosen models		
account for predictors of study results, dose-response models, or		
cumulative meta-analysis) in sufficient detail to be replicated		
Provision of appropriate tables and graphics	Yes	6–7
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Yes	8
Table giving descriptive information for each study included	Yes	8-14
Results of sensitivity testing (e.g., subgroup analysis)	Yes	15–20
Indication of statistical uncertainty of findings	Yes	20
Reporting of discussion should include		1
Quantitative assessment of bias (e.g., publication bias)	Yes	20
Justification for exclusion (e.g., exclusion of non-English language	No	21
citations)		
Assessment of quality of included studies	Yes	Table 1
Strengths and weaknesses	Yes	23
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	Yes	20–23
Generalization of the conclusions (e.g., appropriate for the data	Yes	23
presented and within the domain of the literature review)		
Guidelines for future research	Yes	23
Disclosure of funding source	Yes	24
NA, Not applicable.		<b>I</b>

# **BMJ Open**

# Association of obstructive sleep apnea with the risk of vascular outcomes and all-cause mortality: a meta-analysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2016-013983.R2
Article Type:	Research
Date Submitted by the Author:	19-Sep-2017
Complete List of Authors:	Xie, Chengjuan; The First Affiliated Hospital of Anhui Medical University, Department of Neurology Zhu, Ruolin; The First Affiliated Hospital of Anhui Medical University, Department of Neurology Tian, Yanghua; The First Affiliated Hospital of Anhui Medical University, Department of Neurology Wang, Kai; Department of Neurology
<b>Primary Subject Heading</b> :	Neurology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	meta-analysis, mortality, obstructive sleep apnea, vascular outcome



#### **BMJ Open**

Association of obstructive sleep apnea with the risk of vascular outcomes and all-cause mortality: a meta-analysis

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#### Word count: 6288

#### Abstract

Objective: This study aimed to conduct a meta-analysis to explore and summarize the evidence regarding the association between obstructive sleep apnea (OSA) and the subsequent risk of vascular outcomes and all-cause mortality.

Methods: Electronic databases PubMed, Embase, and the Cochrane Library were searched to identify studies conducted through May 2016. Prospective cohort studies that reported effect estimates with 95% confidence intervals of major adverse cardiac events (MACEs), coronary heart disease (CHD), stroke, cardiac death, all-cause mortality, and heart failure for different levels versus the lowest level of OSA were included.

Results: A total of 16 cohort studies reporting data on 24,308 individuals were included. Of these, 11 studies reported healthy participants, and the remaining 5 studies reported participants with different diseases. Severe OSA was associated with a greater risk of MACEs (P < 0.001), CHD (P = 0.003), stroke (P < 0.001), cardiac death (P = 0.003), and all-cause mortality (P < 0.001); moderate OSA had a harmful impact on MACEs (P = 0.034) and CHD (P = 0.026); and no significant association was found between mild OSA and the risk of vascular outcomes or all-cause mortality (P > 0.05). Finally, no evidence of a factor-specific difference in the risk ratio for MACEs among participants with different levels of OSA compared with those with the lowest level of OSA was found.

Conclusions: Severe and moderate OSAs were associated with an increased risk of

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vascular outcomes and all-cause mortality. This relationship might differ between genders. Therefore, further large-scale prospective studies are needed to verify this difference.

Key words: Meta-analysis; mortality, obstructive sleep apnea, vascular outcome

### Article Summary:

Strengths and limitations of this study:

1. This was a meta-analysis of prospective observational studies designed to elucidate the association of obstructive sleep apnea (OSA) with fatal and nonfatal cardiovascular diseases.

2. The findings were based on a large sample size and are more robust than those obtained from any individual study.

3. The relationship was calculated for subsets of patients with specific characteristics and any potential differences between these subsets were determined.

4. Differently adjusted models might affect the progression of vascular outcomes.

5. Different cutoff values for the apnea–hypopnea index might affect the relationship

between OSA and vascular outcomes.

#### Introduction

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Obstructive sleep apnea (OSA) affects 24% of middle-aged men and 9% of women in the United States, but daytime sleepiness was reported in 17% and 22% of these subjects, respectively [1]. OSA is an increasingly prevalent condition characterized by repetitive obstruction of the upper airway during sleep accompanied by episodic hypoxia, arousal, and sleep fragmentation [2]. Previous studies suggested that OSA was associated with an increased risk of glaucoma, diabetic kidney disease, and metabolic syndrome [3-5]. However, data on the association between OSA and the risk of subsequent vascular outcomes and mortality are both limited and inconclusive. Furthermore, whether these relationships differ according to the characteristics of patients with OSA also needs to be verified.

Several meta-analyses have illustrated that continuous positive airway pressure (CPAP) interventions aimed at OSA may reduce the risk of cardiovascular outcomes. Kim et al. [6] showed that CPAP treatment for OSA was associated with a lower incidence of stroke and cardiac events. Furthermore, Bratton et al. [7] indicated that use of both CPAP and mandibular advancement devices was associated with a reduction in the blood pressure among patients with OSA. Nadeem et al. [8] suggested that CPAP treatment for OSA seemed to improve dyslipidemia (decrease in total cholesterol and low-density lipoprotein, and increase in high-density lipoprotein), whereas it did not appear to affect the triglyceride levels. These studies demonstrated that patients with OSA who received interventions had a reduced risk of cardiovascular diseases. Therefore, clarifying the relationship between OSA and vascular outcomes is particularly important as it has not been definitively determined.

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#### Methods

#### Data sources, search strategy, and selection criteria

This study was conducted and reported according to the Meta-analysis of Observational Studies in Epidemiology protocol [9].

Any prospective cohort study that examined the relationship between OSA and vascular outcomes or all-cause mortality was eligible for inclusion into this study, and no restrictions were placed on language or publication status (e.g., published, in press, or in progress). Electronic databases PubMed, Embase, and the Cochrane Library were searched for articles published through May 2016, using the terms "sleep apnea" OR "obstructive sleep apneas" AND ("cardiovascular disease" OR "stroke" OR "cardiac death" OR "mortality" OR "death" OR "CVD" OR "myocardial infarction" OR "coronary events") AND "clinical trials" AND "human" as the search terms (Supplemental 1). Manual searches of reference lists were also conducted from all the relevant original and reviewed articles to identify additional eligible studies. The medical subject heading, methods, patient population, design, exposure, and outcome variables of these articles were used to identify the relevant studies.

The literature search was independently undertaken by two authors using a standardized approach. Any inconsistencies between these two authors were settled

by the primary author until a consensus was reached. The study was eligible for inclusion if the following criteria were met: (1) the study had a prospective cohort design; (2) the study investigated the association between OSA and the risk of major adverse cardiac events (MACEs), coronary heart disease (CHD), stroke, cardiac death, all-cause mortality, and heart failure; and (3) the authors reported effect estimates [relative risk (RR), hazard ratio (HR), or odds ratio (OR)] and 95% confidence intervals (CIs) for comparisons of different levels of OSA versus lowest OSA level. All case-control studies were excluded because various confounding factors could bias the results.

#### Data collection and quality assessment

The data collected included the first author's name, publication year, country, sample size, mean age at baseline, percentage of male patients, body mass index (BMI), disease status, assessment of OSA, follow-up duration, effect estimate and its 95% CI, reported endpoints, and covariates in the fully adjusted model. For studies that reported several multivariable adjusted RRs, the effect estimate that was maximally adjusted for potential confounders was selected.

The Newcastle–Ottawa Scale (NOS), which is quite comprehensive and has been partially validated for evaluating the quality of observational studies in the meta-analysis, was used to evaluate the methodological quality [10]. The NOS is based on the following three subscales: selection (4 items), comparability (1 item), and outcome (3 items). A "star system" (range, 0–9) was developed for assessment

(Table 1). The data extraction and quality assessment were conducted independently by two authors. Information was examined and adjudicated independently by an additional author referring to the original studies.

#### Statistical analysis

The relationship between OSA and the risk of vascular outcomes or all-cause mortality based on the effect estimate (OR, RR, or HR) and its 95% CI was examined in each study. HR was considered to be equivalent to RR in cohort studies. Given the low incidence of vascular outcomes and all-cause mortality, ORs could be considered as accurate estimates of RRs [11]. A semi-parametric method was first used to evaluate the association of mild OSA [apnea-hypopnea index (AHI): 5-15], moderate OSA (AHI: 15-30) and severe OSA (AHI > 30) with the risk of vascular outcomes or all-cause mortality in order to analyze the trend between OSA levels and vascular outcomes or all-cause mortality risk [12]. For each individual study, each category of AHI was reclassified based on its calculated mid-point (for closed categories) or median (for open categories, assuming a normal distribution for AHI). The control category was composed of participants with the lowest AHI or normal participants in that study. Furthermore, when an individual study provided more than one median AHI level for classification among the three categories (i.e. mild, moderate or severe OSA), a fixed-effects model was used to calculate their summary RRs and 95% CIs to obtain effect estimates for each category [13]. If the study data were not broken down by AHI but rather by oxygen desaturation index (ODI), classification into the OSA categories was carried out based on the judgment of the clinicians. A random-effects

model was then used to calculate summary RRs and 95% CIs for mild, moderate, and severe OSA versus normal [14]. Finally, the ratio of RRs between subgroups (and the corresponding 95% CIs) were estimated using specific RRs and 95% CIs after considering the country, mean age, gender, BMI, disease status, and duration of the follow-up period [15].

Heterogeneity between studies was investigated using the Q statistic, and P values <0.10 was considered as indicative of significant heterogeneity [16 17]. Subgroup analyses were conducted for mild, moderate, and severe OSA and the risk of MACEs based on the country, mean age, gender, BMI, disease status, and duration of the follow-up period. A sensitivity analysis was also performed by removing each individual study from the meta-analysis [18]. Several methods were used to check for potential publication bias. Visual inspections of funnel plots for MACEs were conducted. The Egger [19] and Begg [20] tests were also used to statistically assess publication bias for MACEs. All reported P values were two sided, and P values <0.05 were considered statistically significant for all included studies. Statistical analyses were performed using the STATA software (version 12.0; Stata Corporation, TX, USA).

#### Results

#### Literature search

The results of the study-selection process are shown in Figure 1. An initial electronic search yielded 3282 articles, of which 3236 duplicates and irrelevant

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studies were excluded, and 46 potentially eligible studies were selected. After detailed evaluations, 16 prospective studies were selected for the final meta-analysis [21-36]. No new studies qualified for inclusion after a manual search of the reference lists of these studies. The general characteristics of the included studies are presented in Table 1.

#### Study characteristics

A total of 16 studies with 24,308 individuals qualified for this study. The follow-up period for participants was 2.9–18.0 years, while 73–10,149 individuals were included in each study. Eight studies were conducted in the United States, four in Spain, one in Sweden, one in Portugal, one in Hungary, and one in Canada. Furthermore, 11 studies reported healthy participants, and the remaining 5 studies reported participants with different diseases. The mean BMI ranged from 26.8 to 34.0 kg/m<sup>2</sup>. Fourteen studies used polysomnography (PSG), and the remaining one study used limited PSG to assess the levels of OSA. The study quality was assessed using the NOS (Table 1). Overall, one study had a score of 9, six studies had a score of 8, seven studies had a score of 7, and the remaining two studies had a score of 6.

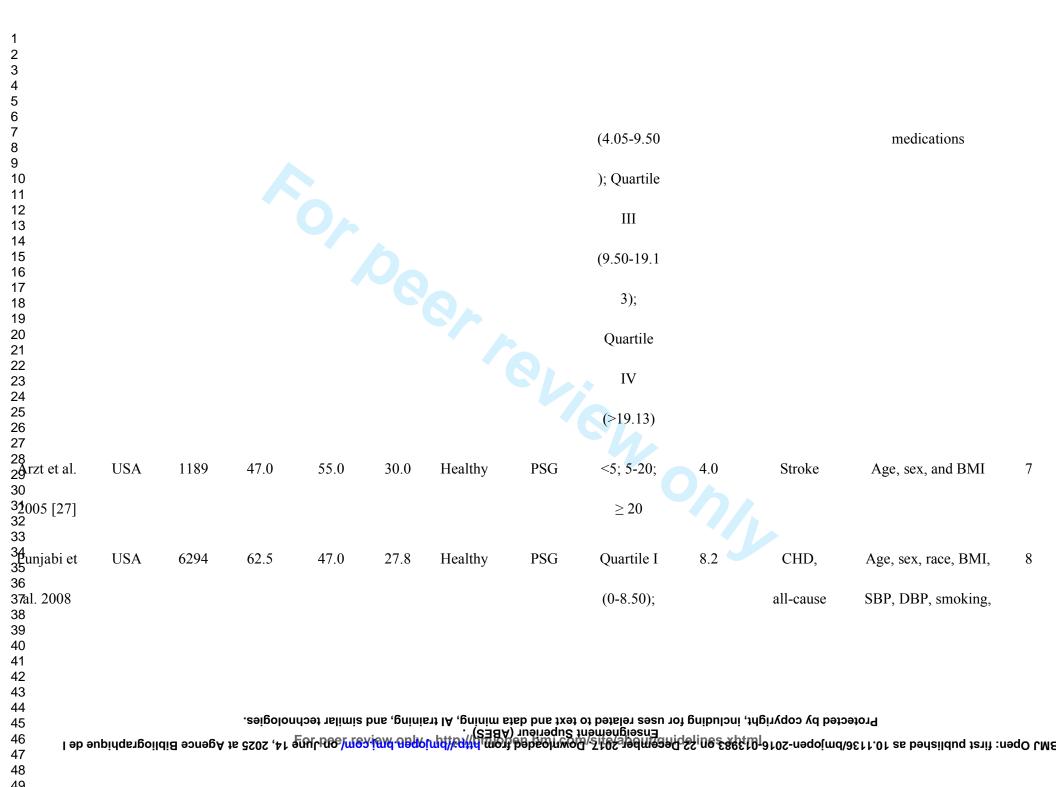
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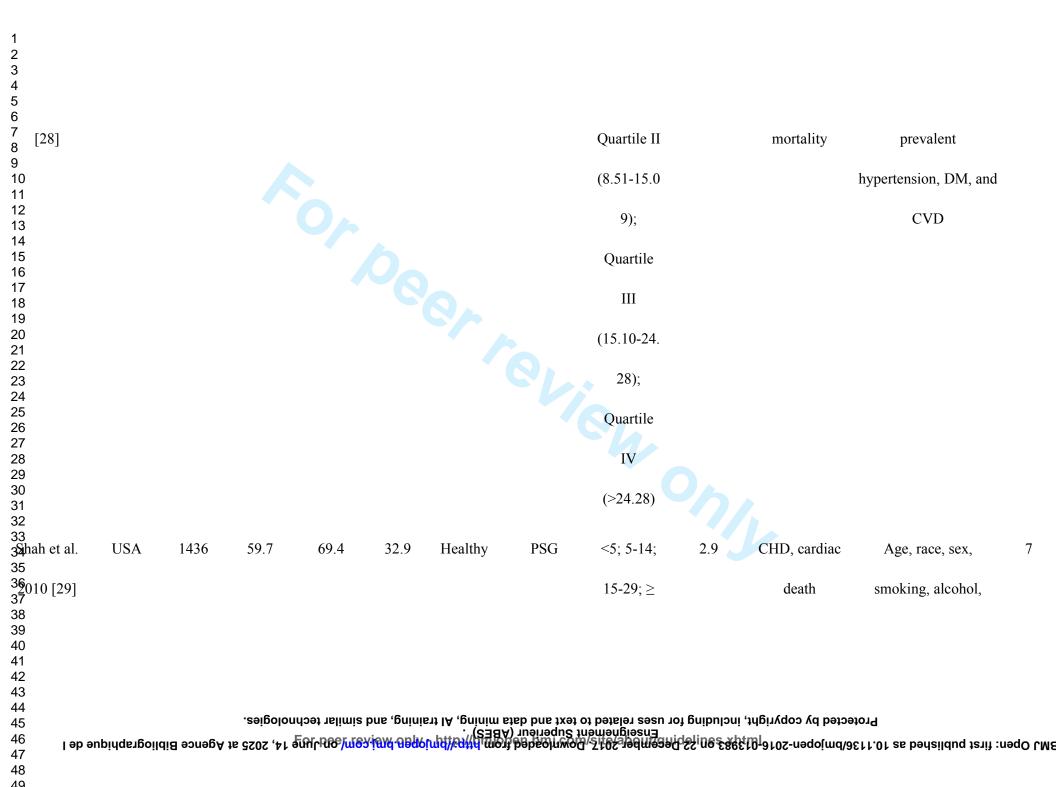
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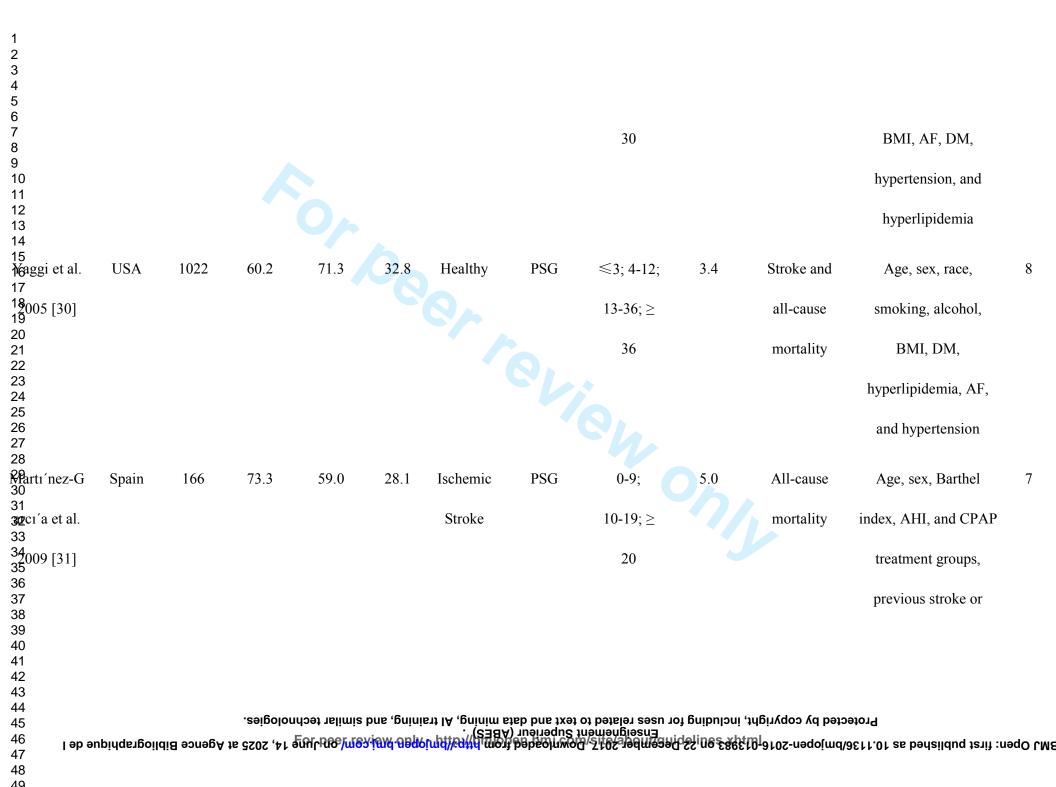
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7 8			Table 1	. Baseline ch	aracteristi	c of studies	included in the	systematic re	eview and me	ta-analysis		
9												
10 11 Study 12	Country	Sample	Mean	Percenta	BMI	Disease	Assessment	AHI or	Follow-up	Reported	Adjusted factors	NOS
13 14		size	age	ge male		status	OSA	ODI	duration	outcomes		score
15 16 17				(%)				categories	(year)			
18 19400e et al. 20	Sweden	408	59.1	58.4	27.0	CAD	Limited	< 5; 5-10;	5.1	CHD, stroke,	Age, sex, BMI,	7
21 2 <b>2</b> 000 [21]							PSG	10-15; ≥		all-cause	hypertension, DM,	
23 24 25 26								15		mortality	LVF, and coronary	
27											intervention	
28 29												
300 ottlieb et 31	USA	4422	62.4	43.5	28.2	Healthy	PSG	< 5; 5-15;	8.7	HF	Age, race, BMI,	8
32 33 <sup>a</sup> l. 2010 34								15-30; ≥			smoking, DM, SBP,	
35 [22] 36								30			DBP, TC, HDL-C,	
37 38											lipid-lowering	
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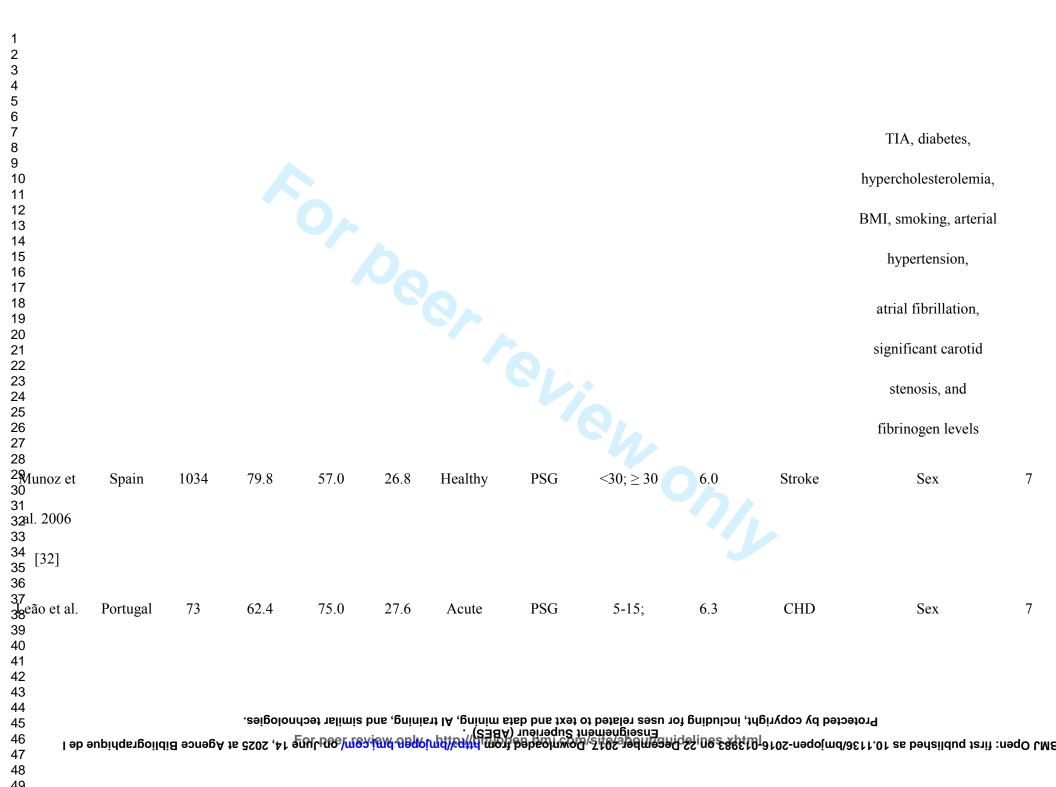
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$\mathbf{G}$ impos-Ro Spain 1116 56.1 0.0 36.6 Healthy PSG < 10; 6.0 Cardiac death Age, BM 17	1I, DM, 8
$18 riguez et 10-29; \ge 10-29; = 10-29;$	ion, and
20 21al 2012 30 previou	s CVD
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9 10 11											and use of	
12 13											antihypertensive,	
14 15 16											lipid-lowering and	
17 18 19											antidiabetic drugs	
20 <b>Xo</b> ung et al. 22	USA	1522	48.0	55.0	28.6	Healthy	PSG	5-15;	18.0	Cardiac death,	Age, age-squared, sex,	8
23 24 <sup>008</sup> [25]								15-30; ≥		all-cause	BMI, and	
25 26 27								30		mortality, and	BMI squared	
28 29 30										CHD		
31 3 <u>R</u> edline et 33	USA	5422	62.9	45.4	27.8	Healthy	PSG	Quartile I	8.7	Stroke	Age, BMI, race,	8
34 <sub>al.</sub> 2010								(0-4.05);			smoking, SBP, DM,	
36 37 [26] 38								Quartile II			and antihypertensive	
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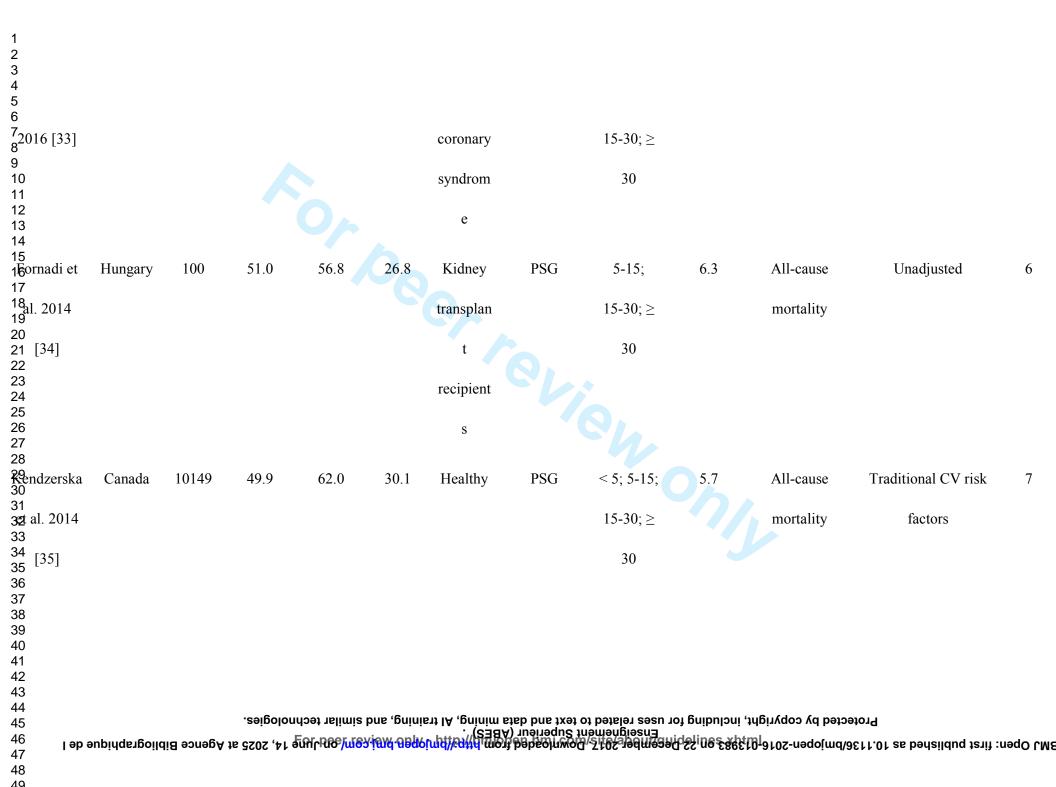








Page 17 of 56





#### **OSA** and MACE risk

Table 2. Summary of the relative risks of all outcomes evaluated

19 of 56	BMJ Open								
	OSA and MACE risk								
	OSA unu MACL HSK								
	The summary RRs	showed that	mild OSA was not a	associated with	MACEs (RR:				
	<i> j</i>				(				
	0.98; 95% CI: 0.87–1	$11 \cdot P = 0.7$	41. Fig. 2 and Table	2) Furthermo	ore the nooled	i			
	0.90, 9570 CI. $0.07-1$	.11, 1 = 0.7	41, Fig. 2 and Table	<i>2)</i> . Purtifering	ne, the pooled				
	1	1	004 11 11	4.44.1.1.1.	1				
	analysis results for mo	derate and s	evere OSA indicated	that they had a	harmful effect				
						-			
	on the risk of MACEs	(moderate: F	RR, 1.16; 95% CI, 1.0	P = 0.0000000000000000000000000000000000	034; Fig. 3 and				
						ι.			
	Table 2; severe: RR,	2.04; 95% 0	CI, 1.56–2.66; $P < 0$	.001; Fig. 4 ai	nd Table 2). A	3			
	subgroup analysis for	MACEs wa	s conducted to minin	nize heterogene	eity among the				
				C		Ű			
	included studies and e	valuate the	relationship between	OSA and MA	CEs in specific				
	meradea staares and e	variance the h			ells in specific	Ģ			
	subpopulations (Table	3) Overall	participants with m	odarata OSA y	vara associated				
	subpopulations (Table	5). Overall,	participants with m	ouerate OSA v	vere associated				
				.1 1	(DD 11)				
	with an increased risk	of MACES 1	f individuals did not l	have other disea	ases (RR: 1.16;				
	95% CI: 1.01–1.33; P	95% CI: 1.01–1.33; $P = 0.034$ ). Furthermore, no significant association was found							
	between severe OSA and MACEs if the study included only women (RR: 1.98; 95%								
	CI: $0.64-6.06; P = 0$	.234); in ot	her subsets, severe (	OSA was asso	ciated with an	ų			
	increased risk of MA	ACEs (Tabl	e 3). Finally, no e	vidence of a	factor-specific				
	difference was found i	n the RR fo	r MACEs among par	ticipants with (	OSA compared	u l			
					-	ŝ			
	with controls (Table 3)								
	( )								
	Table 2. Su	mmary of the	e relative risks of all o	outcomes evalu	ated				
Outcomes	Mild OSA (RR	P value	Moderate OSA	P value for	Severe OSA	P va			
		- ,							
	with 95% CI)	for mild	(RR with 95%	moderate	(RR with 95%	for sev			
	with 5570 CI	ior minu		mourate	(IXIX WILLI 9570	101 501			
		OSA	CI)	OSA	CI)	06			
		USA	CI)	USA	CI)	05/			
						for sev OSA <0.00			
		0 741	1 16 (1 01 1 22)	0.024	2.04(1.56, 2.66)				
MACEs	0.98 (0.87–1.11)	0.741	1.16 (1.01–1.33)	0.034	2.04 (1.56-2.66)	<0.00			

CH	łD	1.25 (0.95–1.66)	0.117	1.38	(1.04–1.83)		0.026	1.63 (1.18–2.26)	0.003
Stro	oke	1.29 (0.69–2.41)	0.424	1.35	(0.82–2.23)		0.245	2.15 (1.42–3.24)	<0.00
Cardia	c death	1.80 (0.68–4.76)	0.236	1.11	(0.53–2.35)		0.781	2.96 (1.45-6.01)	0.008t
All-cause	mortality	1.26 (0.77–2.07)	0.354	1.04	(0.60–1.79)		0.895	1.54 (1.21–1.97)	ظ م الح <0.08
Heart	failure	1.02 (0.78–1.34)	0.868	1.07	(0.74–1.54)		0.719	1.44 (0.94–2.21)	Prot $\mathfrak{B}$ ted by copyright, including for uses
	CH	D, Coronary heart	disease;	CI: confid	ence interval	l; MAC	E, major c	ardiovascular	cluding
	eve	nt; OSA, obstructiv	ve sleep a	pnea; RR:	relative risk.				for us
									for uses related
			Table 3.	Subgroup	analyses for	MACE	Ès		ated to
Variabl	Subgroup	Mild OS	A (RR	P value	Moderate	OSA	P value	Severe OSA	P var
e		with 95%	CI)	for mild	(RR with	95%	for	(RR with 95%	for data
				OSA	CI)		moderate	CI)	sever
							OSA		g, Al trai
Country	USA	1.00 (0.85	5–1.17)	0.977	1.14 (0.99–	-1.32)	0.064	1.90 (1.35–2.67)	
	Other	1.02 (0.19	9–5.52)	0.982	1.44 (0.83-	-2.50)	0.198	2.35 (1.52–3.65)	< 0.00 <sup>T</sup> and similar t
	USA vs of	ther 0.98 (0.18	3-5.32)	0.982	0.79 (0.45-	-1.40)	0.422	0.81 (0.46–1.41)	0.45300000000000000000000000000000000000
Mean	≥60	0.96 (0.86	6–1.08)	0.540	1.13 (0.97–	-1.33)	0.117	1.78 (1.23–2.57)	0.002 <sup>.008</sup> .
age	<60	1.40 (0.73	3–2.70)	0.315	1.51 (0.94-	-2.41)	0.086	2.31 (1.64–3.24)	<0.001
	≥60 vs <6	0 0.69 (0.35	5–1.33)	0.265	0.75 (0.46-	-1.23)	0.252	0.77 (0.47–1.27)	0.309

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1 2 3								
4 5	Gender	Male	0.92 (0.73–1.15)	0.455	1.10 (0.85–1.42)	0.449	1.81 (1.14–2.89)	0.012
6 7 8		Female	1.97 (0.47–8.25)	0.353	1.36 (0.67–2.76)	0.399	1.98 (0.64–6.06)	0.234 a
9 10 11		Male vs female	0.47 (0.11–1.99)	0.304	0.81 (0.38–1.72)	0.581	0.91 (0.27–3.08)	0.885 <b>cted</b>
12 13 14 15	BMI	≥30	1.75 (0.88–3.49)	0.111	1.70 (0.94–3.07)	0.079	2.72 (1.80-4.10)	0.8855ted by sopyrigh
16 17 18		<30	0.96 (0.86–1.07)	0.449	1.14 (0.99–1.31)	0.078	1.80 (1.36–2.38)	<0.001 inc
19 20 21		≥30 vs <30	1.82 (0.91–3.66)	0.092	1.49 (0.81–2.74)	0.198	1.51 (0.92–2.49)	0.104 g for
22 23 24	Disease	Healthy	1.00 (0.85–1.17)	0.977	1.16 (1.01–1.33)	0.034	2.12 (1.53–2.94)	<0.00 s ra
25 26 27	statues	Other	1.02 (0.19–5.52)	0.982	_	-	1.96 (1.01–3.81)	9 gnement S 9.047d to to
28 29 30		Healthy vs	0.98 (0.18–5.32)	0.982		-	1.08 (0.52–2.27)	0.835 and
31 32 33		Other						ur (ABE data mi
34 35 36	Follow-	≥6	0.96 (0.86–1.07)	0.449	1.14 (0.99–1.31)	0.064	2.06 (1.43-2.95)	nin <0.004 A
37 38 39	up	<6	1.75 (0.88–3.49)	0.111	1.74 (0.87–3.49)	0.120	2.10 (1.39–3.17)	<0.001
40 41 42	duration	≥6 vs <6	0.55 (0.27–1.10)	0.092	0.66 (0.32–1.33)	0.242	0.98 (0.57–1.70)	0.945 similar technologies.
43 44 45		BMI, body	mass index; CI: c	onfidence i	nterval; OSA, obst	ructive slee	p apnea; RR:	lar tec
45 46 47 48 49		relative risl	K.					hnologies.

### **OSA** and CHD risk

The pooled data of meta-analysis showed that mild OSA was not associated with the risk of CHD (RR: 1.25; 95% CI: 0.95–1.66; *P* = 0.117; Table 2 and Supplemental 2), whereas moderate OSA (RR: 1.38; 95% CI: 1.04–1.83; P = 0.026; Table 2 and

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	Supplementa	l 2) and severe OS.	A (RR: 1.	63; 95% CI: 1.18–	2.26; $P = 0$ .	003; Table 2			
	and Supplem	and Supplemental 2) were associated with a significantly increased risk of CHD.							
	Stratified and	alyses according to	gender v	vere conducted for	different le	vels of OSA	Prote		
	versus norma	ll group, and it was	found tha	t patients with seve	re OSA had	significantly	ected by		
	increased the	risk of CHD in me	n (RR: 1.6	65; 95% CI: 1.06–2	.57; P = 0.02	27). No other	у соруг		
	significant di	fferences were dete	cted (Tab	le 4).			ight, in		
		Table 4. Ge	ender diffe	erence for other out	comes		Protected by copyright, including fo		
Outcome	Subgroup	Mild OSA (RR	<i>P</i> value	Moderate OSA	P value	Severe OSA (RR	P ves re		
		with 95% CI)	for	(RR with 95%	for	with 95% CI)	related		
			mild	CI)	moderate		seven x		
			OSA		OSA		ong data		
CHD	Men	0.93 (0.72–1.21)	0.596	1.09 (0.80–1.48)	0.582	1.65 (1.06–2.57)	a m¥ing, 0.		
	Women	1.92 (0.43-8.64)	0.394	1.51 (0.38–5.97)	0.559	1.10 (0.12–9.87)	Algrainii		
	Men vs women	0.48 (0.11–2.22)	0.351	0.72 (0.18–2.96)	0.651	1.50 (0.16–14.22)	ng.7and		
Stroke	Men	1.86 (0.67–5.14)	0.232	1.86 (0.70-4.95)	0.214	2.86 (1.10-7.41)	sim∰ar te		
	Women	1.34 (0.76–2.36)	0.311	1.20 (0.67–2.15)	0.542	1.21 (0.65–2.25)	nga 0.7and sim <b>B</b> ar technologies. 0.500 0.138		
	Men vs women	1.39 (0.43–4.45)	0.581	1.55 (0.50–4.84)	0.451	2.36 (0.76–7.38)	ng 0.7a4 0.7and sim <b>0.6</b> ar technologies. 0.138 0.02		
Cardiac	Men	_	_	1.15 (0.41–3.23)	0.791	2.87 (1.13–7.27)	0.02		
death	Women	_	_	0.94 (0.19–4.61)	0.939	3.71 (0.41–33.87)	0.245		

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3 4 5		Men vs women	-	_	1.22 (0.18-8.17)	0.935	0.77 (0.07–8.49)	0.834
6 7 8	All-cause	Men	_	_	_	_	1.72 (1.22–2.43)	0.002
9 10 11	mortality	Women	-	_	_	_	3.50 (1.23–9.97)	Protes
12 13 14 15		Men vs women	-	_	_	_	0.49 (0.16–1.48)	0.2000 0.2000 0.000 0.000
16 17 18	Heart	Men	0.88 (0.57–1.35)	0.561	1.13 (0.68–1.88)	0.639	1.58 (0.93–2.67)	ig <b>1</b> 88 0. <b>6</b> 78 inc
19 20 21	failure	Women	1.13 (0.80–1.60)	0.493	1.01 (0.60–1.70)	0.970	1.19 (0.56–2.52)	including for
22 23 24		Men vs women	0.78 (0.45–1.35)	0.376	1.12 (0.54–2.32)	0.762	1.33 (0.53–3.33)	or uses re 0.5es re

CHD, coronary heart disease; OSA, obstructive sleep apnea.

#### **OSA** and stroke risk

Pooled analysis results indicated no association between mild OSA (RR: 1.29; 95% CI: 0.69-2.41; P = 0.424; Table 2 and Supplemental 2) and moderate OSA (RR: 1.35; 95% CI: 0.82–2.23; P = 0.245; Table 2 and Supplemental 2) and stroke, whereas severe OSA was associated with an increased risk of stroke (RR: 2.15; 95% CI: 1.42-3.24; P < 0.001; Table 2 and Supplemental 2). Subgroup analysis on the basis of gender indicated that severe OSA had a harmful effect on the risk of stroke in men (RR: 2.86; 95% CI: 1.10–7.41; P = 0.031; Table 4).

### **OSA** and cardiac death risk

The summary RRs showed that mild OSA (RR: 1.80; 95% CI: 0.68–4.76; P =0.236; Table 2 and Supplemental 2) and moderate OSA (RR: 1.11; 95% CI: 0.53–2.35; P = 0.781; Table 2 and Supplemental 2) were not associated with cardiac death risk, whereas severe OSA significantly increased the risk of cardiac death (RR: 2.96; 95% CI: 1.45–6.01; P = 0.003; Table 2 and Supplemental 2). Subgroup analysis showed that severe OSA was associated with an increased risk of cardiac death in men (RR: 2.87; 95% CI: 1.13–7.27; *P* = 0.026; Table 4).

### **OSA** and all-cause mortality risk

No significant association was found between mild OSA (RR: 1.26; 95% CI: 0.77-2.07; P = 0.354; Table 2 and Supplemental 2), moderate OSA (RR: 1.04; 95%) CI: 0.60–1.79; P = 0.895; Table 2 and Supplemental 2), and all-cause mortality risk. However, severe OSA had a harmful impact on the all-cause mortality (RR: 1.54; 95% CI: 1.21–1.97; P < 0.001; Table 2 and Supplemental 2). Stratified analysis suggested that severe OSA increased the risk of all-cause mortality in men (RR: 1.72; 95% CI: 1.22–2.43; P = 0.002) and women (RR: 3.50; 95% CI: 1.23–9.97; P = 0.019; Table 4).

#### **OSA** and heart failure risk

The summary results indicated no significant differences between mild OSA (RR: 1.02; 95% CI: 0.78–1.34; P = 0.868), moderate OSA (RR: 1.07; 95% CI: 0.74–1.54; P = 0.719), and severe OSA (RR: 1.44; 95% CI: 0.94–2.21; P = 0.097), and the risk of heart failure (Table 2 and Supplemental 2). Subgroup analysis reported similar results compared with the overall analysis (Table 4).

#### **Publication bias**

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Review of the funnel plots could not rule out the potential publication bias for MACEs (Fig. 5). The Egger and Begg test results showed no evidence of publication bias for MACEs of mild OSA (*P* value for Egger: 0.132; *P* value for Begg: 0.221) and moderate OSA (*P* value for Egger: 0.052; *P* value for Begg: 0.452). Although the Begg test showed no evidence of publication bias for MACEs of severe OSA (*P* = 0.118), the Egger test showed potential evidence of publication bias for MACEs of severe OSA (*P* < 0.001). The conclusion did not change after adjustment for publication bias using the trim-and-fill method [37].

#### Discussion

The present study was based on prospective cohort studies and explored all possible correlations between OSA and the outcomes of MACEs, CHD, stroke, cardiac death, all-cause mortality, and heart failure. This large quantitative study included 24,308 individuals from 16 prospective cohort studies with a broad range of populations. The findings from the present meta-analysis suggested that mild OSA had no significant impact on the risk of vascular outcomes and all-cause mortality, moderate OSA was associated with an increased risk of MACEs and CHD, and severe OSA had a harmful effect on the risk of MACEs, CHD, stroke, cardiac death, and all-cause mortality.

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A previous meta-analysis suggested that OSA was associated with stroke, but its relationship with ischemic heart disease and cardiovascular mortality needs further research [38]. However, this study could not illustrate the impact of different levels of OSA on the risk of serious cardiovascular outcomes. Further, Dong et al. suggested

that moderate-to-severe OSA significantly increased the risk of cardiovascular diseases, in particular, the risk of stroke [39]. Similarly, Ge et al. indicated that severe OSA is a strong independent predictor of cardiovascular and all-cause mortality. CPAP treatment was associated with decreased cardiovascular mortality [40]. However, these two studies could not evaluate the association of OSA with the risk of vascular outcomes and all-cause mortality in specific subpopulations. In addition, Wang et al. suggested that severe OSA significantly increased the risk of CHD and stroke, and all-cause mortality. A positive association with CHD was observed for moderate OSA but not for mild OSA [41]. However, whether this relationship differs according to the characteristics of participants remains unclear. Finally, Xie et al. conducted a meta-analysis to evaluate the relationship between OSA and recurrent vascular events and all-cause mortality [42]. However, they just compared the highest AHI versus lowest AHI, whereas the degree of OSA and subsequent adverse outcomes were not available. Therefore, a comprehensive meta-analysis of these prospective cohort studies was performed to evaluate any possible correlates between OSA and vascular outcomes.

No significant difference was observed between mild OSA and the risk of vascular outcomes. However, several studies included in this study reported inconsistent results. Young et al. suggested that mild OSA significantly increased the risk of CHD by 92% [25], whereas Punjabi et al. indicated that mild OSA might have a harmful effect on the risk of CHD [28]. This might be because these two studies used healthy individuals as controls, which may make them more susceptible to acquired

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significant conclusion. Furthermore, most of these studies did not take into account potential confounders for the risk of cardiovascular disease. Moderate-to-severe OSA might play an important role in the risk of vascular outcomes. Shah et al. concluded that OSA increased the risk of coronary events or death from cardiovascular causes [29]. Nearly all included studies reported adverse outcomes for severe OSA. Finally, Previous studies indicated that OSA was a cause of diabetes, which was an independent risk factor for MACEs [43].

Subgroup analyses reported similar conclusions. Gender might have an impact on the relationship between OSA and CHD, stroke, or cardiac death, although the sex difference was not statistically significant. The possible reasons could be the lower prevalence of severe OSA in women and the later age of onset of OSA in women than in men. Furthermore, OSA in women always occurred after menopause. Physiological response to OSA is another reason for this nonsignificant difference. Finally, these conclusions might be unreliable because smaller cohorts were included in each subset. Therefore, further large-scale studies were needed to verify this difference. Therefore, a relative result was given, and a synthetic and comprehensive review was provided.

No significant difference was found between mild or moderate OSA and all-cause mortality, while severe OSA was associated with an increased risk of all-cause mortality. Further, these significant associations were also observed in men and women separately. Although the effect estimate in women was larger than that in men, no gender difference was found in the relationship between OSA and all-cause mortality. This might be because the number of studies that reported the relationship

between severe OSA and all-cause mortality was smaller than expected, and a broad 95% CI was acquired. Therefore, the association of severe OSA with all-cause mortality in women was variable and should be verified in future large-scale prospective studies.

Three strengths of this study should be highlighted. First, only prospective studies were included, which eliminated selection and recall bias, and could be of concern in retrospective case-control studies. Second, the large sample size allowed us to quantitatively assess the association of OSA with the risk of vascular outcomes and mortality, and thus the findings were potentially more robust than those of any individual study. Third, the summary RRs were calculated to evaluate any potential difference between subsets according to the characteristics of participants.

The limitations of this study were as follows: (1) the adjusted models were different across the included studies, and these factors might have played an important role in developing vascular outcomes; (2) in a meta-analysis of published studies, publication bias was an inevitable problem; and (3) the analysis used pooled data (individual data were not available), which restricted performing a more detailed relevant analysis and obtaining more comprehensive results.

The results of this study suggested that moderate-to-severe OSA might play an important role in the risk of vascular outcomes, especially for men. Future studies should focus on specific populations to analyze the gender difference to study the association between OSA and vascular outcomes.

### **Author Contributions**

Chengjuan Xie carried out the studies, participated in collecting data, and drafted the manuscript. Ruolin Zhu performed the statistical analysis and participated in its design. Yanghua Tian and Kai Wang helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of interests: All authors declare no conflict of interest.

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Data sharing statement: No additional data available.

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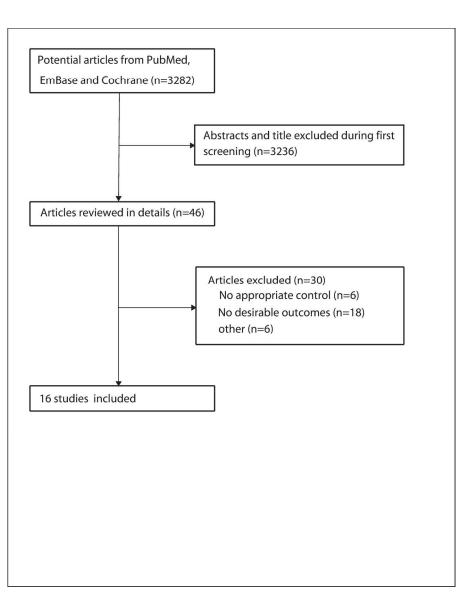
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## **Figure legends:**

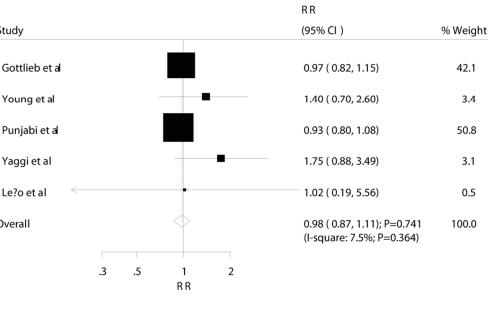
- Figure 1. Study-selection process.
- Figure 2. Association between mild OSA and MACEs.
- Figure 3. Association between moderate OSA and MACEs.
- Figure 4. Association between severe OSA and MACEs.

Figure 5. Funnel plots.



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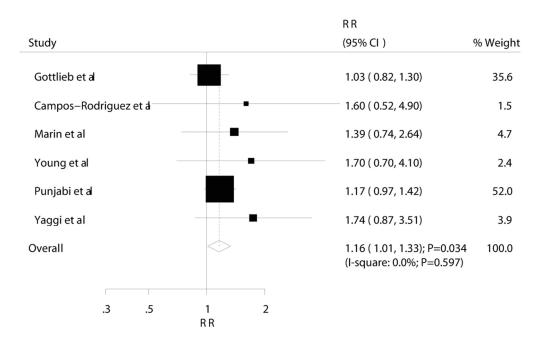
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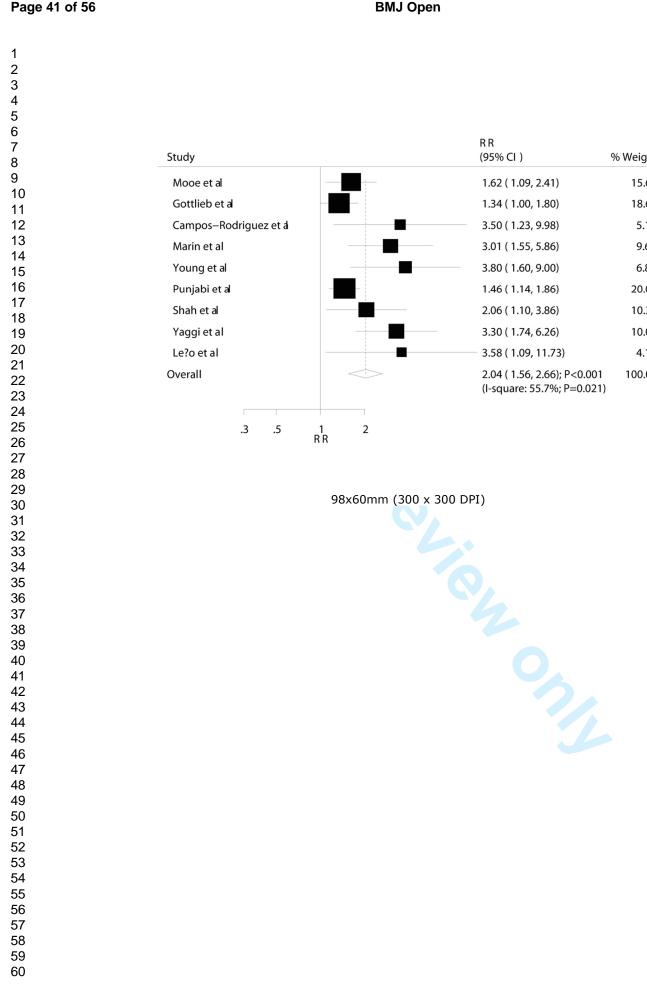
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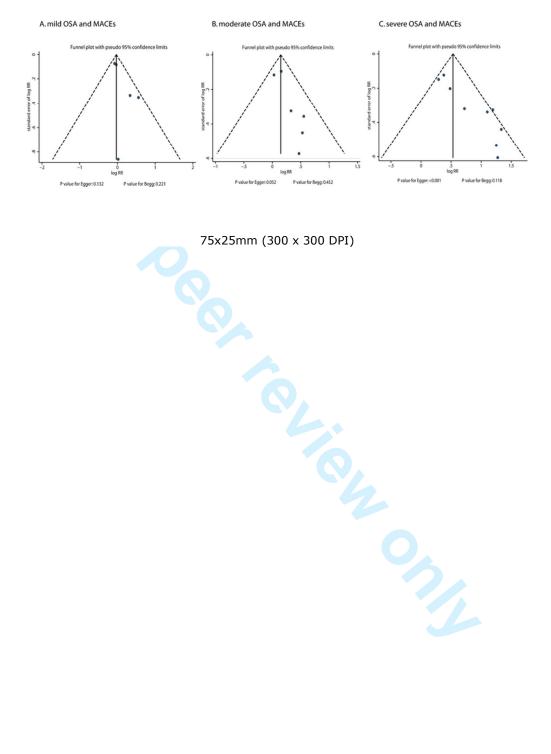
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	Primary Sleep Apneas of Newborn OR Newborn Primary Sleep Apneas OR Centra
	Sleep Apnea, Primary OR Primary Central Sleep Apnea
#7	"Continuous Positive Airway Pressure" [Mesh] OR "CPAP" [All fields] Ol
	"Continuous Positive Airway Pressure/therapy" [Mesh]
#8	CPAP Ventilation OR Ventilation, CPAP OR Biphasic Continuous Positive Airwa
	Pressure OR Bilevel Continuous Positive Airway Pressure OR Nasal Continuou
	Positive Airway Pressure OR nCPAP Ventilation OR Ventilation, nCPAP OI
	Airway Pressure Release Ventilation OR APRV Ventilation Mode OR APRV
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<b>#9</b>	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	"Cardiovascular System" [Mesh]
#11	"Death" [Mesh] OR Determination of Death OR Near-Death Experience OR
	Cardiac Death OR Death, Cardiac OR "Mortality" [Mesh] OR "mortality" [All
	fields] OR "Disease" [Mesh] OR "disease*"
#12	#10 AND #11
#13	"Cardiovascular Diseases" [Mesh] OR "CVD" OR Cardiovascular Disease OR
	Disease, Cardiovascular OR Diseases, Cardiovascular
#14	"Myocardial Infarction" [Mesh] OR "MI" OR Infarction, Myocardial OR
	Infarctions, Myocardial OR Myocardial Infarctions OR Cardiovascular Stroke OR
	Cardiovascular Strokes OR Stroke, Cardiovascular OR Strokes, Cardiovascular OR
	Heart Attack OR Heart Attacks OR Myocardial Infarct OR Infarct, Myocardial OR
	Infarcts, Myocardial OR Myocardial Infarcts
#15	"Angina Pectoris" [Mesh] OR "Angina, Stable" [Mesh] OR "Microvascular
	Angina" [Mesh] OR "Angina, Unstable" [Mesh] OR Stenocardia OR Stenocardias
	OR Angor Pectoris OR "angina" [All fields] OR "Coronary Artery Disease" [Mesh]
	OR "CAD" OR "ischemic heart disease" [All fields] OR "Heart Failure" [Mesh]
	OR "Heart Failure, Diastolic" [Mesh] OR "Heart Failure, Systolic" [Mesh]
#16	"Cerebrovascular Disorders" [Mesh] OR "cerebrovascular" [All fields] OR
	"stroke*"
#17	"Death" [Mesh] OR Determination of Death OR Near-Death Experience OR
	Cardiac Death OR Death, Cardiac OR "Mortality" [Mesh] OR "mortality" [All
	fields] OR "mortality*"
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	"Prospective Studies" [Mesh] OR "Cohort Studies" [Mesh] OR "Follow-Up
	Studies" [Mesh] OR "prospective study" OR "cohort study" OR "follow-up study"
#20	#9 AND #18 AND #19

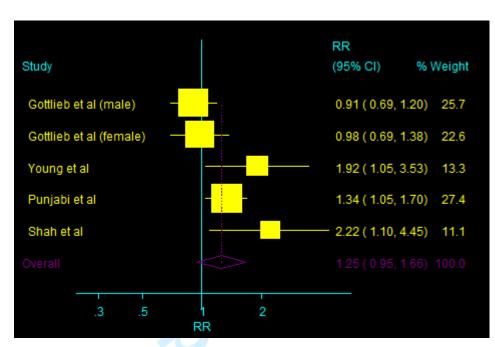
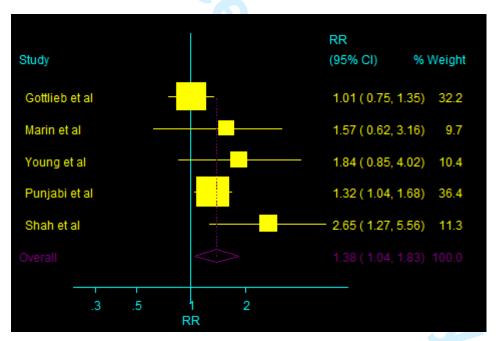


Figure S1. Association between mild OSA and CHD.



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Figure S2. Association between moderate OSA and CHD.

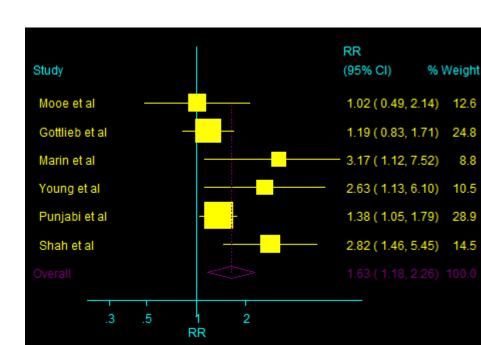


Figure S3. Association between severe OSA and CHD.

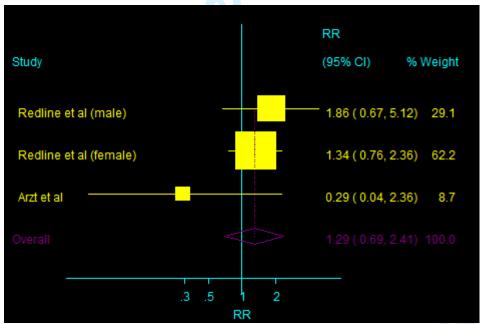
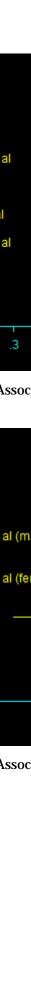


Figure S4. Association between mild OSA and stroke.



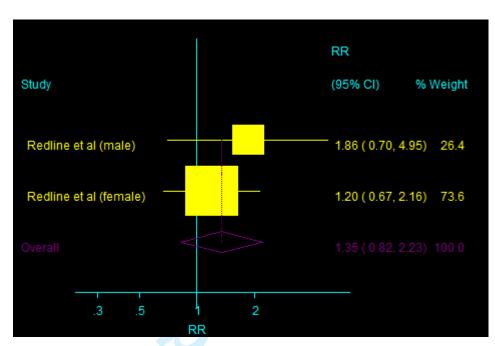


Figure S5. Association between moderate OSA and stroke.

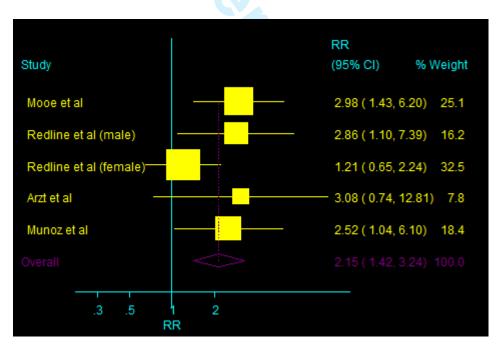
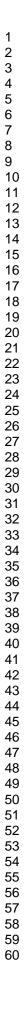


Figure S6. Association between severe OSA and stroke

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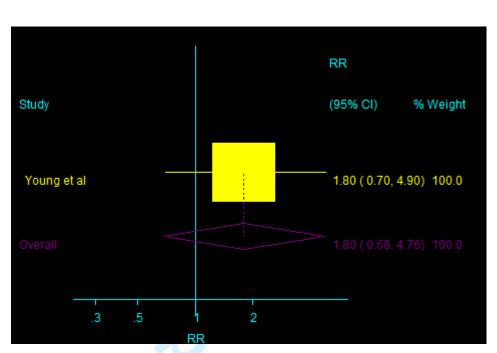
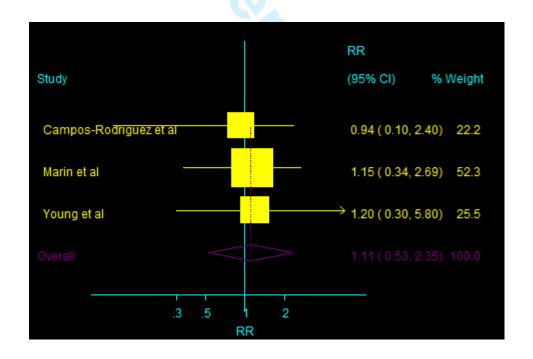
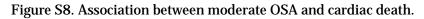


Figure S7. Association between mild OSA and cardiac death.





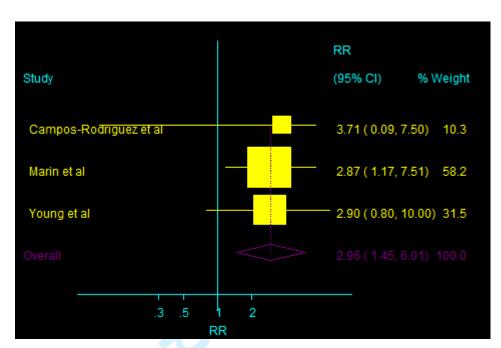
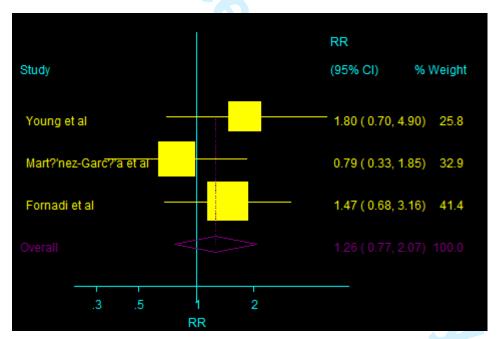


Figure S9. Association between severe OSA and cardiac death.



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Figure S10. Association between mild OSA and all-cause death.

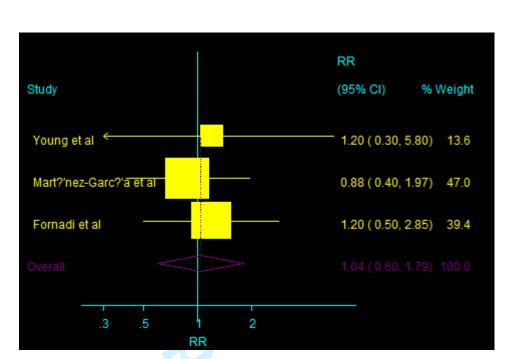


Figure S11. Association between moderate OSA and all-cause death.

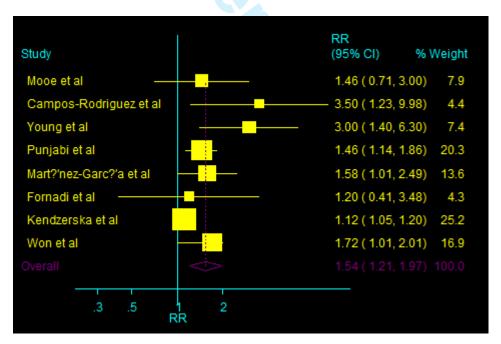


Figure S12. Association between severe OSA and all-cause death.

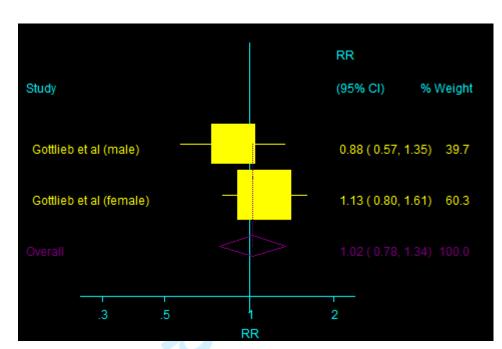


Figure S13. Association between mild OSA and heart failure.

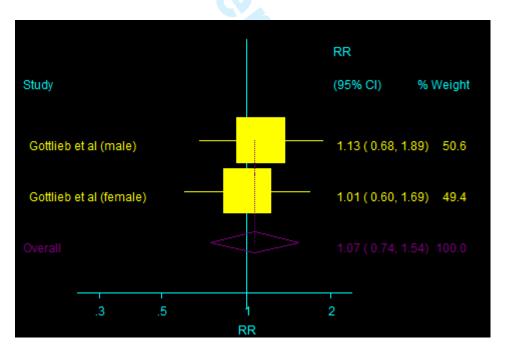


Figure S14. Association between moderate OSA and heart failure.

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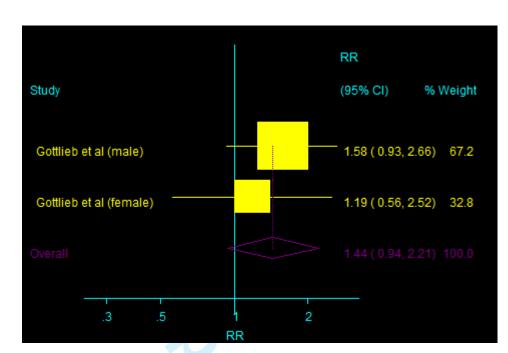


Figure S15. Association between severe OSA and heart failure.

**BMJ Open** 

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Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			3-4
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			4-7
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	<ul> <li>(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</li> <li>Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</li> <li>Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants</li> <li>(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed</li> <li>Case-control study—For matched studies, give matching criteria and the number of controls per case</li> </ul>	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	7
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed	7

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			7-20
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	( <i>a</i> ) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			21-23
Key results	18	Summarise key results with reference to study objectives	22
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies. Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# MOOSE Statement: Reporting Checklist for Authors, Editors, and Reviewers of Meta-

# analyses of Observational Studies

Reporting Criteria	Reported (Yes/No)	Reported on Page
Reporting of background should include		
Problem definition	Yes	3
Hypothesis statement	Yes	3
Description of study outcomes	Yes	3
Type of exposure or intervention used	Yes	3 - 4
Type of study designs used	Yes	4
Study population	Yes	4
Reporting of search strategy should include		
Qualifications of searchers (e.g., librarians and investigators)	Yes	4 - 5
Search strategy, including time period used in the synthesis and key words	Yes	5
Effort to include all available studies, including contact with authors	Yes	5
Databases and registries searched	Yes	4–5
Search software used, name and version, including special features used (e.g., explosion)	Yes	4-5
Use of hand searching (e.g., reference lists of obtained articles)	Yes	5
List of citations located and those excluded, including justification	Yes	8
Method of addressing articles published in languages other than English	Yes	4
Method of handling abstracts and unpublished studies	Yes	4–5
Description of any contact with authors	No	NA
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	No	5
Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	Yes	5–6
Documentation of how data were classified and coded (e.g., multiple raters, blinding and inter-rater reliability)	Yes	56
Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	Yes	6
Assessment of study quality, including blinding of quality assessors, and stratification or regression on possible predictors of study results	Yes	6

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Assessment of heterogeneity	Yes	7
Description of statistical methods (e.g., complete description of fixed- or random-effects models, justification of whether the chosen models account for predictors of study results, dose–response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	6–7
Provision of appropriate tables and graphics	Yes	6–7
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Yes	8
Table giving descriptive information for each study included	Yes	8-14
Results of sensitivity testing (e.g., subgroup analysis)	Yes	15–20
Indication of statistical uncertainty of findings	Yes	20
Reporting of discussion should include		
Quantitative assessment of bias (e.g., publication bias)	Yes	20
Justification for exclusion (e.g., exclusion of non-English language citations)	No	21
Assessment of quality of included studies	Yes	Table 1
Strengths and weaknesses	Yes	23
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	Yes	20–23
Generalization of the conclusions (e.g., appropriate for the data presented and within the domain of the literature review)	Yes	23
Guidelines for future research	Yes	23
Disclosure of funding source	Yes	24

# **BMJ Open**

# Association of obstructive sleep apnea with the risk of vascular outcomes and all-cause mortality: a meta-analysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2016-013983.R3
Article Type:	Research
Date Submitted by the Author:	10-Oct-2017
Complete List of Authors:	Xie, Chengjuan; The First Affiliated Hospital of Anhui Medical University, Department of Neurology Zhu, Ruolin; The First Affiliated Hospital of Anhui Medical University, Department of Neurology Tian, Yanghua; The First Affiliated Hospital of Anhui Medical University, Department of Neurology Wang, Kai; Department of Neurology
<b>Primary Subject Heading</b> :	Neurology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	meta-analysis, mortality, obstructive sleep apnea, vascular outcome



#### BMJ Open

Association of obstructive sleep apnea with the risk of vascular outcomes and all-cause mortality: a meta-analysis

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#### Word count: 6288

Abstract

Objective: This study aimed to conduct a meta-analysis to explore and summarize the evidence regarding the association between obstructive sleep apnea (OSA) and the subsequent risk of vascular outcomes and all-cause mortality.

Methods: Electronic databases PubMed, Embase, and the Cochrane Library were searched to identify studies conducted through May 2016. Prospective cohort studies that reported effect estimates with 95% confidence intervals of major adverse cardiac events (MACEs), coronary heart disease (CHD), stroke, cardiac death, all-cause mortality, and heart failure for different levels versus the lowest level of OSA were included.

Results: A total of 16 cohort studies reporting data on 24,308 individuals were included. Of these, 11 studies reported healthy participants, and the remaining 5 studies reported participants with different diseases. Severe OSA was associated with an increased risk of MACEs (relative risk [RR]: 2.04; 95%CI: 1.56–2.66; P < 0.001), CHD (RR: 1.63; 95%CI: 1.18–2.26; P = 0.003), stroke (RR: 2.15; 95%CI: 1.42–3.24; P < 0.001), cardiac death (RR: 2.96; 95%CI: 1.45–6.01; P = 0.003), and all-cause mortality (RR: 1.54; 95%CI: 1.21–1.97; P < 0.001). Moderate OSA was also significantly associated with increased risk of MACEs (RR: 1.16; 95%CI: 1.01–1.33; P = 0.034) and CHD (RR: 1.38; 95%CI: 1.04–1.83; P = 0.026). No significant association was found between mild OSA and the risk of vascular outcomes or all-cause mortality (P > 0.05). Finally, no evidence of a factor-specific difference in

the risk ratio for MACEs among participants with different levels of OSA compared with those with the lowest level of OSA was found.

Conclusions: Severe and moderate OSAs were associated with an increased risk of vascular outcomes and all-cause mortality. This relationship might differ between genders. Therefore, further large-scale prospective studies are needed to verify this difference.

Key words: Meta-analysis; mortality, obstructive sleep apnea, vascular outcome

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#### **Article Summary:**

Strengths and limitations of this study:

1. This was a meta-analysis to elucidate the association of obstructive sleep apnea (OSA) with fatal and nonfatal cardiovascular diseases, using a broad search strategy and predefined selection criteria and with no restriction of language or publication status.

2. The methodological quality of each study was assessed using the Newcastle-Ottawa Scale for prospective observational studies, and a meta-analysis, sensitivity analysis, subgroup analysis and bias assessment were also conducted.

3. Only prospective studies were included, eliminating selection and recall bias that could be of concern in retrospective case-control studies.

4. Summary relative risks were calculated to evaluate any potential difference between subsets according to the characteristics of the participants.

5. Different cutoff values for the apnea-hypopnea index might affect the relationship between OSA and vascular outcomes.

 Obstructive sleep apnea (OSA) affects 24% of middle-aged men and 9% of women in the United States, but daytime sleepiness was reported in 17% and 22% of these subjects, respectively [1]. OSA is an increasingly prevalent condition characterized by repetitive obstruction of the upper airway during sleep accompanied by episodic hypoxia, arousal, and sleep fragmentation [2]. Previous studies suggested that OSA was associated with an increased risk of glaucoma, diabetic kidney disease, and metabolic syndrome [3-5]. However, data on the association between OSA and the risk of subsequent vascular outcomes and mortality are both limited and inconclusive. Furthermore, whether these relationships differ according to the characteristics of patients with OSA also needs to be verified.

Several meta-analyses have illustrated that continuous positive airway pressure (CPAP) interventions aimed at OSA may reduce the risk of cardiovascular outcomes. Kim et al. [6] showed that CPAP treatment for OSA was associated with a lower incidence of stroke and cardiac events. Furthermore, Bratton et al. [7] indicated that use of both CPAP and mandibular advancement devices was associated with a reduction in the blood pressure among patients with OSA. Nadeem et al. [8] suggested that CPAP treatment for OSA seemed to improve dyslipidemia (decrease in total cholesterol and low-density lipoprotein, and increase in high-density lipoprotein), whereas it did not appear to affect the triglyceride levels. These studies demonstrated that patients with OSA who received interventions had a reduced risk of cardiovascular diseases. Therefore, clarifying the relationship between OSA and

vascular outcomes is particularly important as it has not been definitively determined. This study attempted to perform a large-scale examination of the available prospective studies to determine the association of OSA with the potential risk of vascular outcomes and all-cause mortality.

### Methods

#### Data sources, search strategy, and selection criteria

This study was conducted and reported according to the Meta-analysis of Observational Studies in Epidemiology protocol (Checklist S1) [9].

Any prospective cohort study that examined the relationship between OSA and vascular outcomes or all-cause mortality was eligible for inclusion into this study, and no restrictions were placed on language or publication status (e.g., published, in press, or in progress). Electronic databases PubMed, Embase, and the Cochrane Library were searched for articles published through May 2016, using the terms "sleep apnea" OR "obstructive sleep apneas" AND ("cardiovascular disease" OR "stroke" OR "cardiac death" OR "mortality" OR "death" OR "CVD" OR "myocardial infarction" OR "coronary events") AND "clinical trials" AND "human" as the search terms (Supplemental 1). Manual searches of reference lists were also conducted from all the relevant original and reviewed articles to identify additional eligible studies. The medical subject heading, methods, patient population, design, exposure, and outcome variables of these articles were used to identify the relevant studies.

The literature search was independently undertaken by two authors using a standardized approach. Any inconsistencies between these two authors were settled by the primary author until a consensus was reached. The study was eligible for inclusion if the following criteria were met: (1) the study had a prospective cohort design; (2) the study investigated the association between OSA and the risk of major adverse cardiac events (MACEs), coronary heart disease (CHD), stroke, cardiac death, all-cause mortality, and heart failure; and (3) the authors reported effect estimates [relative risk (RR), hazard ratio (HR), or odds ratio (OR)] and 95% confidence intervals (CIs) for comparisons of different levels of OSA versus lowest OSA level. All case-control studies were excluded because various confounding factors could bias the results.

## Data collection and quality assessment

The data collected included the first author's name, publication year, country, sample size, mean age at baseline, percentage of male patients, body mass index (BMI), disease status, assessment of OSA, follow-up duration, effect estimate and its 95% CI, reported endpoints, and covariates in the fully adjusted model. For studies that reported several multivariable adjusted RRs, the effect estimate that was maximally adjusted for potential confounders was selected.

The Newcastle–Ottawa Scale (NOS), which is quite comprehensive and has been partially validated for evaluating the quality of observational studies in the meta-analysis, was used to evaluate the methodological quality [10]. The NOS is

based on the following three subscales: selection (4 items), comparability (1 item), and outcome (3 items). A "star system" (range, 0–9) was developed for assessment (Table 1). The data extraction and quality assessment were conducted independently by two authors. Information was examined and adjudicated independently by an additional author referring to the original studies.

#### Statistical analysis

The relationship between OSA and the risk of vascular outcomes or all-cause mortality based on the effect estimate (OR, RR, or HR) and its 95% CI was examined in each study. HR was considered to be equivalent to RR in cohort studies. Given the low incidence of vascular outcomes and all-cause mortality, ORs could be considered as accurate estimates of RRs [11]. A semi-parametric method was first used to evaluate the association of mild OSA [apnea-hypopnea index (AHI): 5-15], moderate OSA (AHI: 15-30) and severe OSA (AHI > 30) with the risk of vascular outcomes or all-cause mortality in order to analyze the trend between OSA levels and vascular outcomes or all-cause mortality risk [12]. For each individual study, each category of AHI was reclassified based on its calculated mid-point (for closed categories) or median (for open categories, assuming a normal distribution for AHI). The control category was composed of participants with the lowest AHI or normal participants in that study. Furthermore, when an individual study provided more than one median AHI level for classification among the three categories (i.e. mild, moderate or severe OSA), a fixed-effects model was used to calculate their summary RRs and 95% CIs to obtain effect estimates for each category [13]. If the study data were not broken down

by AHI but rather by oxygen desaturation index (ODI), classification into the OSA categories was carried out based on the judgment of the clinicians. A random-effects model was then used to calculate summary RRs and 95% CIs for mild, moderate, and severe OSA versus normal [14]. Finally, the ratio of RRs and the corresponding 95% CIs between subgroups were estimated using specific RRs and 95% CIs in each group based on the country, mean age, gender, BMI, disease status, and duration of the follow-up period [15].

Heterogeneity between studies was investigated using the Q statistic, and *P* values <0.10 was considered as indicative of significant heterogeneity [16 17]. Subgroup analyses were conducted for mild, moderate, and severe OSA and the risk of MACEs based on the country, mean age, gender, BMI, disease status, and duration of the follow-up period. A sensitivity analysis was also performed by removing each individual study from the meta-analysis [18]. Several methods were used to check for potential publication bias. Visual inspections of funnel plots for MACEs were conducted. The Egger [19] and Begg [20] tests were also used to statistically assess publication bias for MACEs. All reported *P* values were two sided, and *P* values <0.05 were regarded as statistically significant for all included studies. Statistical analyses were performed using the STATA software (version 12.0; Stata Corporation, TX, USA).

3MJ Open: first published as 10.1136/bmjopen-2016-013983 on 22 December 2017. Downloaded from http://bmjopen.bmj.com/ on June 14, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

### Results

#### Literature search

The results of the study-selection process are shown in Figure 1. An initial electronic search yielded 3282 articles, of which 3236 duplicates and irrelevant studies were excluded, and 46 potentially eligible studies were selected. After detailed evaluations, 16 prospective studies were selected for the final meta-analysis [21-36]. No new studies qualified for inclusion after a manual search of the reference lists of these studies. The general characteristics of the included studies are presented in Table 1.

### Study characteristics

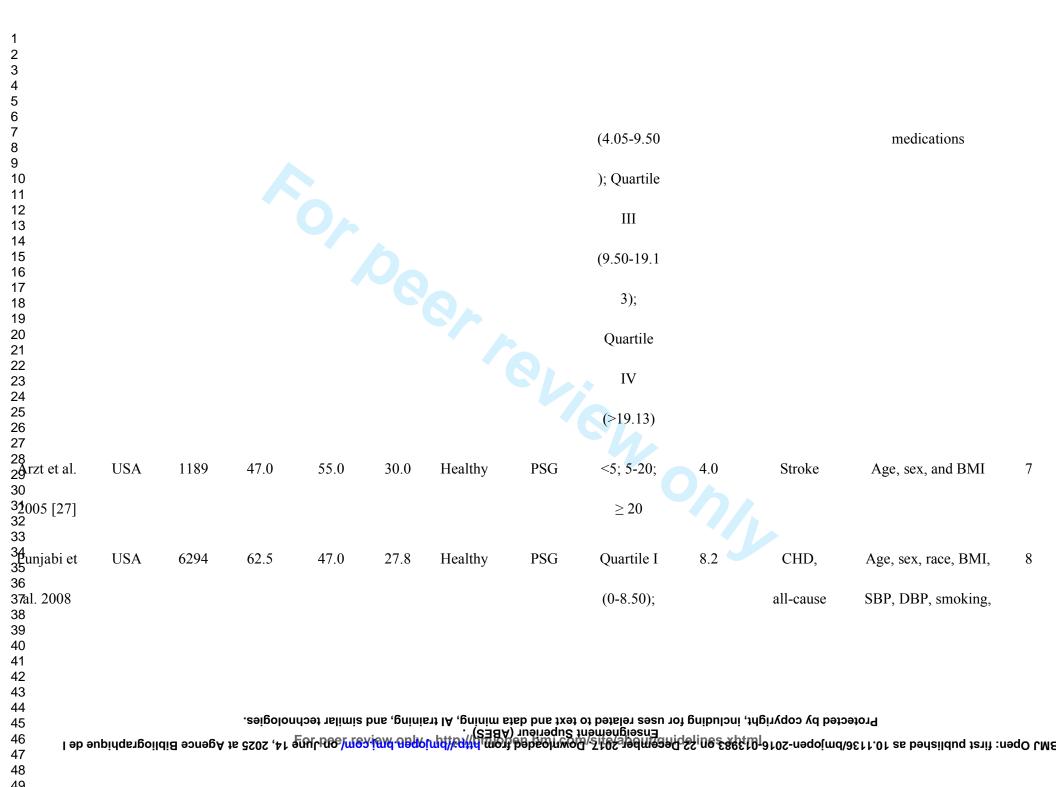
A total of 16 studies with 24,308 individuals qualified for this study. The follow-up period for participants was 2.9–18.0 years, while 73–10,149 individuals were included in each study. Eight studies were conducted in the United States, four in Spain, one in Sweden, one in Portugal, one in Hungary, and one in Canada. Furthermore, 11 studies reported healthy participants, and the remaining 5 studies reported participants with different diseases. The mean BMI ranged from 26.8 to 34.0 kg/m<sup>2</sup>. Fourteen studies used polysomnography (PSG), and the remaining one study used limited PSG to assess the levels of OSA. The study quality was assessed using the NOS (Table 1). Overall, one study had a score of 9, six studies had a score of 8, seven studies had a score of 7, and the remaining two studies had a score of 6.

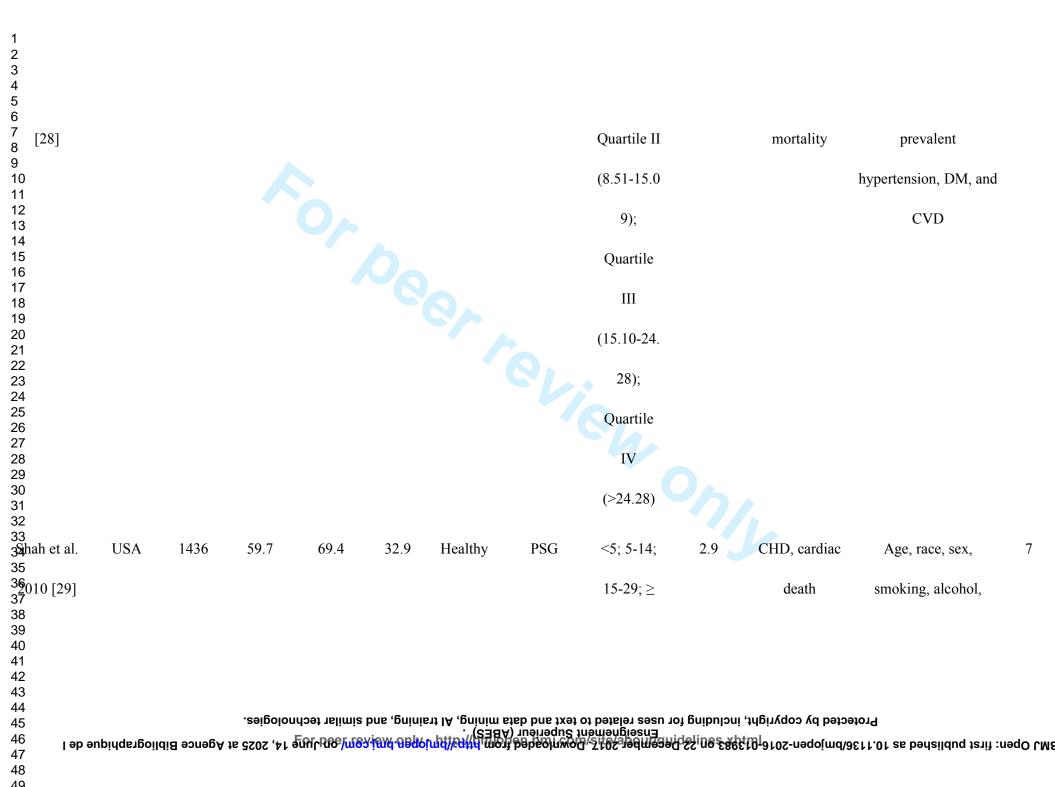
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6 7 8			Table 1	. Baseline ch	aracteristic	c of studies	included in the	systematic re	eview and me	ta-analysis		
9 10 11 Study	Country	Sample	Mean	Percenta	BMI	Disease	Assessment	AHI or	Follow-up	Reported	Adjusted factors	NOS
12 13 14		size	age	ge male		status	OSA	ODI	duration	outcomes		score
15 16 17				(%)				categories	(year)			
18 19100e et al. 20	Sweden	408	59.1	58.4	27.0	CAD	Limited	< 5; 5-10;	5.1	CHD, stroke,	Age, sex, BMI,	7
21 2 <del>2</del> 000 [21]							PSG	10-15; ≥		all-cause	hypertension, DM,	
23 24 25								15		mortality	LVF, and coronary	
26 27 28											intervention	
29 30ottlieb et 31	USA	4422	62.4	43.5	28.2	Healthy	PSG	< 5; 5-15;	8.7	HF	Age, race, BMI,	8
32 33 <sup>a</sup> l. 2010								15-30; ≥			smoking, DM, SBP,	
34 35 [22] 36 37								30			DBP, TC, HDL-C,	
38											lipid-lowering	
39 40 41												
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44 45 46 Lan			.səipolo	l similar techn	one ,eninie	BES)'', uttal	IA) Therieur (IA) o text and data	Enseighethe bafalared i	, including for	cteq py copyright	Prote	
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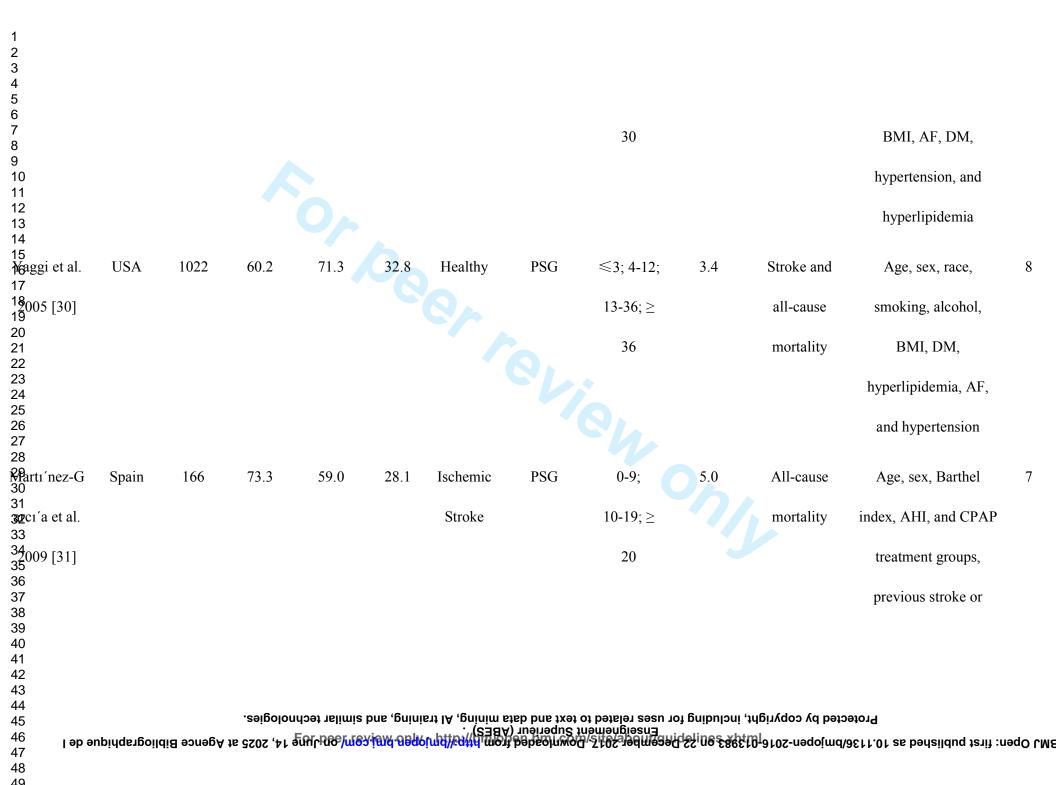
Page 12 of 55

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9 10 11												antihypertensive	
12 13												medications	
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Gampos-F 17	Ro Spa	un	1116	56.1	0.0	36.6	Healthy	PSG	< 10;	6.0	Cardiac death	Age, BMI, DM,	8
18 19 19	et								10-29; ≥			hypertension, and	
20 21al. 2012									30			previous CVD	
22 23 24 [23] 25 26 24 26													
25													
Aarin et a 28	al. Spa	uin	1729	49.9	100	28.7	Healthy	PSG	$5-30; \geq 30$	10.1	Cardiac death	Age, diagnostic group,	9
<sup>29</sup> 2005 [24	]										and CHD	presence of CVD, DM,	
31 32 33												hypertension, lipid	
33 34 35												disorders, smoking,	
36 37												alcohol, SBP DBP,	
38 39													
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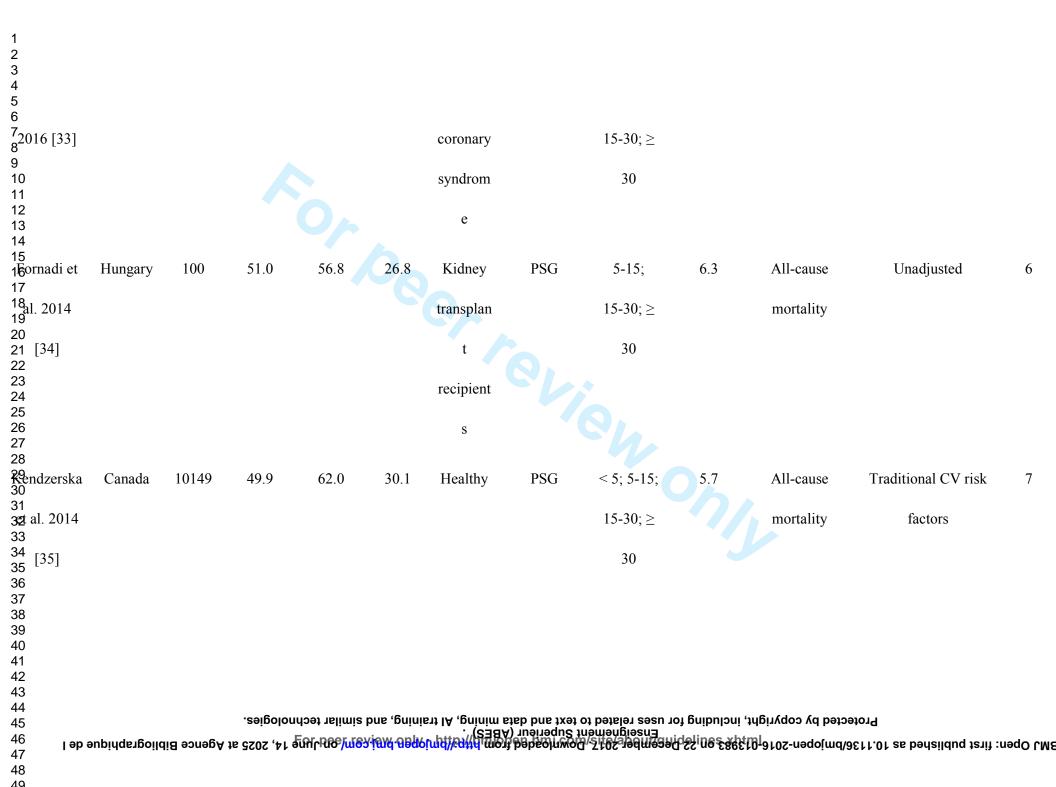
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11 12 13											antihypertensive,	
14 15											lipid-lowering and	
16 17 18 19											antidiabetic drugs	
20 2⁄0ung et al. 22	USA	1522	48.0	55.0	28.6	Healthy	PSG	5-15;	18.0	Cardiac death,	Age, age-squared, sex,	8
23 24 <sup>008</sup> [25]								15-30; ≥		all-cause	BMI, and	
25 26 27								30		mortality, and	BMI squared	
28 29 30										CHD		
31 3 <u>R</u> edline et 33	USA	5422	62.9	45.4	27.8	Healthy	PSG	Quartile I	8.7	Stroke	Age, BMI, race,	8
34 <sub>al.</sub> 2010								(0-4.05);			smoking, SBP, DM,	
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17 18 19											atrial fibrillation,			
20 21 22											significant carotid			
23 24											stenosis, and			
25 26 27											fibrinogen levels			
28 29 Junoz et 30 31 32al. 2006 33 34 35 36	Spain	1034	79.8	57.0	26.8	Healthy	PSG	<30; ≥ 30	6.0	Stroke	Sex	7		
37 38eão et al. 39 40 41 42 43	Portugal	73	62.4	75.0	27.6	Acute	PSG	5-15;	6.3	CHD	Sex	7		
44 45 46 <b>J əp a</b> 47 48 49	ənpidqargoild	li <b>B ə</b> ənəgA	א 14, 2025 at נוסוסקופא.	ອັນປຸປເ <u>ດຣ</u> ັງແຂອ ອັນປຸດເວລາຍາຍ ອີນປັດສາມອາຊາຍ	Ajak-9994 Ajak July	Pinna∰on (Pinna) ABES) Brinim (BES) Brinim (Pinnim )	), bəbsolruq 1, bəbsolruq 4) rufinər 4) suğu buşta 1, buş buşta	g, 21, 24, 29, 24, 29, 24, 24, 24, 24, 24, 24, 24, 24, 24, 24	t, including fo	β <mark>1</mark> ∂102-n∍qoįmd βη∂102-n∍qoimd	/3611.01 as bədailduq first Protec	aqO LM8		





#### **OSA** and MACE risk

Table 2. Summary of the relative risks of all outcomes evaluated

			BMJ Open			Page 2								
	OSA and MACE risk					Page 2								
	The summary RRs	showed that	mild OSA was not a	associated with	MACEs (RR:									
	0.98; 95% CI: 0.87-1	.11; $P = 0.7$	41; Fig. 2 and Table	e 2). Furthermo	ore, the pooled	Protected by copyright, including for uses related to text and da								
	analysis results for mo	analysis results for moderate and severe OSA indicated that they had a harmful effect												
	on the risk of MACEs	on the risk of MACEs (moderate: RR, 1.16; 95% CI, 1.01–1.33; $P = 0.034$ ; Fig. 3 and												
	Table 2; severe: RR,	Table 2; severe: RR, 2.04; 95% CI, 1.56–2.66; P < 0.001; Fig. 4 and Table 2). A												
	subgroup analysis for	ubgroup analysis for MACEs was conducted to minimize heterogeneity among the												
	included studies and evaluate the relationship between OSA and MACEs in specific													
	subpopulations (Table	3). Overall,	participants with me	oderate OSA w	vere associated	s relate								
	with an increased risk of MACEs if individuals did not have other diseases (RR: 1.16;													
	95% CI: 1.01–1.33; P	e = 0.034). I	Furthermore, no sign	ificant associat	ion was found	xt and								
	between severe OSA a	and MACEs	if the study included	only women (	RR: 1.98; 95%	data mi								
	CI: $0.64-6.06; P = 0$	.234); in ot	her subsets, severe (	OSA was asso	ciated with an	ining, A								
	increased risk of Ma	ACEs (Tabl	e 3). Finally, no e	vidence of a	factor-specific	l traini								
	difference was found i	n the RR fo	r MACEs among par	ticipants with (	OSA compared	, Al training, and								
	with controls (Table 3)					simila								
	Table 2. Sur	mmary of the	e relative risks of all o	outcomes evalu	ated	ta mining, Al training, and similar technologies.								
Outcomes	Mild OSA (RR	P value	Moderate OSA	P value for	Severe OSA	P vale								
	with 95% CI)	for mild	(RR with 95%	moderate	(RR with 95%	for sever								
		OSA	CI)	OSA	CI)	OSA								
MACEs	0.98 (0.87–1.11)	0.741	1.16 (1.01–1.33)	0.034	2.04 (1.56-2.66)	< 0.001								

i ag	6 21 01 33						DIVIJ	Open				(	õ		
1 2													ven: first		
- 3 4 5	С	HD	1.25 (0	.95–1.66)	0.11	7	1.38 (1.04–1.83)			0.026	1.63 (1.18–2.26)	0.003	hublish		
6 7 8	Stroke		1.29 (0	.69–2.41)	0.42	4	1.35	(0.82–2.23)		0.245 2.15	2.15 (1.42–3.24)	< 0.001	ed as 10.		
9 10 11	Cardiac death 1		1.80 (0	.68–4.76)	0.23	6	1.11	(0.53–2.35)		0.781	2.96 (1.45-6.01)	Protected by copyright, including for uses	Open: first bublished as 10.1136/bmiopen-2016-013983		
12 13 14	All-caus	e mortality	1.26 (0	.77–2.07)	0.35	4	1.04	(0.60–1.79)		0.895	1.54 (1.21–1.97)	<0.0 <b>6</b> 1	iopen-201		
15 16 17 18	Hear	t failure	1.02 (0	0.78–1.34) 0.868		8 1.07 (0.74–1.54)				0.719	1.44 (0.94–2.21)	right 0.0977 inc	16-01398;		
19 20	CHD, Coronary heart disease; CI: confidence interval; MACE, major cardiovascular														
21 22 23	event; OSA, obstructive sleep apnea; RR: relative risk.														
24 25 26	Table 3. Subgroup analyses for MACEs														
27 28 29	Variable	Subgroup		Mild OSA	(RR	Р	value	Moderate	OSA	P value	Severe OSA (RR	P At a	Downloaded		
30 31 32				with 95% C	I)	for	mild	(RR with 9:	5% CI)	for	with 95% CI)		_		
33 34 35							<b>X</b>			moderate		(ABES) . OSA nining, Al t	om http		
36 37 38								4		OSA		Al train	://bmiod		
39 40 41	Country	USA		1.00 (0.85–1	.17)	0.97	7	1.14 (0.99–	1.32)	0.064	1.90 (1.35–2.67)	< 0.00 <sup>1</sup> and	en.bmi.c		
42 43 44		Other		1.02 (0.19-5	5.52)	0.98	2	1.44 (0.83–	2.50)	0.198	2.35 (1.52–3.65)	< 0.00 sinular 1	om/ on		
45 46 47		USA vs oth	er	0.98 (0.18-5	5.32)*	0.98	2	0.79 (0.45–	1.40)*	0.422	0.81 (0.46–1.41)*	<b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.0</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b> <b>c0.00</b>	June 14.		
48 49 50	Mean	≥60		0.96 (0.86–1	.08)	0.54	0	1.13 (0.97–	1.33)	0.117	1.78 (1.23–2.57)	<u>gi</u> 0.002 <sup>.</sup>	2025 at		
51 52 53	age	<60		1.40 (0.73–2	2.70)	0.31	5	1.51 (0.94–	2.41)	0.086	2.31 (1.64–3.24)	<0.001	Agence E		
54 55 56 57 58		≥60 vs <60		0.69 (0.35–1	1.33)*	0.26	5	0.75 (0.46–1.23)*		0.252	0.77 (0.47–1.27)*	0.309	niopen.bmi.com/ on June 14. 2025 at Agence Bibliographique de l		
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Page 22 of 55 Open : fi

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Gender	Male	0.92 (0.73–1.15)	0.455	1.10 (0.85–1.42)	0.449	1.81 (1.14–2.89)	0.012 blishe
	Female	1.97 (0.47–8.25)	0.353	1.36 (0.67–2.76)	0.399	1.98 (0.64–6.06)	0.234 83 P
	Male vs female	0.47 (0.11–1.99)*	0.304	0.81 (0.38–1.72)*	0.581	0.91 (0.27–3.08)*	0.234 as 10.1136/bmjopen-2016-013983
BMI	≥30	1.75 (0.88–3.49)	0.111	1.70 (0.94–3.07)	0.079	2.72 (1.80-4.10)	open-201 <0.00€opyr
	<30	0.96 (0.86–1.07)	0.449	1.14 (0.99–1.31)	0.078	1.80 (1.36–2.38)	6-013983 <0.00∰ incl
	≥30 vs <30	1.82 (0.91–3.66)*	0.092	1.49 (0.81–2.74)*	0.198	1.51 (0.92–2.49)*	0.104 ng f
Disease	Healthy	1.00 (0.85–1.17)	0.977	1.16 (1.01–1.33)	0.034	2.12 (1.53–2.94)	December Enseig or u <del>se</del> s rei
statues	Other	1.02 (0.19–5.52)	0.982	_	-	1.96 (1.01–3.81)	0.047 tr
	Healthy vs Other	0.98 (0.18–5.32)*	0.982	<u> </u>	-	1.08 (0.52–2.27)*	Downloaded nt Superieur 0.835 and da
Follow-	≥6	0.96 (0.86–1.07)	0.449	1.14 (0.99–1.31)	0.064	2.06 (1.43-2.95)	<0.00 <sup>11</sup> (ABE mir
up	<6	1.75 (0.88–3.49)	0.111	1.74 (0.87–3.49)	0.120	2.10 (1.39–3.17)	Ning_Al training 0.945
duration	≥6 vs <6	0.55 (0.27–1.10)*	0.092	0.66 (0.32–1.33)*	0.242	0.98 (0.57–1.70)*	aining, a
	BMI, body	mass index; CI: c	onfidence i	nterval; OSA, obst	ructive sleep	o apnea; RR:	nd sin
<ul> <li>relative risk. * Reported as ratio of RR and 95% CI.</li> </ul>							√ on Ju nilar te
	OSA and C	CHD risk					.bmj.com/ on June 14, 202 , and similar technologies
	The pool	led data of meta-ar	nalysis shov	ved that mild OSA	was not as	sociated with	)25 at A
the risk of CHD (RR: 1.25; 95% CI: 0.95–1.66; $P = 0.117$ ; Table 2 and Supplemental						Supplemental	gence
3 2), whereas moderate OSA (RR: 1.38; 95% CI: 1.04–1.83; $P = 0.026$ ; Table 2 and 5							Bibliog
	Supplemen	tal 2) and severe O	9SA (RR: 1	.63; 95% CI: 1.18–	2.26; $P = 0$ .	003; Table 2	. <mark>bmj.com/</mark> on June 14, 2025 at Agence Bibliographique de l , and similar technologies.
	Disease statues Follow-	FemaleMale vs femaleBMI≥30≥30 vs <30	Female $1.97 (0.47-8.25)$ Male vs female $0.47 (0.11-1.99)^*$ BMI $\geq 30$ $1.75 (0.88-3.49)$ $\leq 30$ $0.96 (0.86-1.07)$ $\geq 30 vs < 30$ $1.82 (0.91-3.66)^*$ Disease       Healthy $1.00 (0.85-1.17)$ statues       Other $1.02 (0.19-5.52)$ Healthy vs Other $0.98 (0.18-5.32)^*$ Follow- $\geq 6$ $0.96 (0.86-1.07)$ up $< 6$ $0.96 (0.86-1.07)$ up $< 6$ $0.96 (0.86-1.07)$ up $< 6$ $0.55 (0.27-1.10)^*$ BMI, body mass index; CI: c       relative risk. * Reported as rat <i>OSA and CHD risk</i> The pooled data of meta-an         the risk of CHD (RR: 1.25; 95) $2$ ), whereas moderate OSA (1)	Female       1.97 (0.47-8.25)       0.353         Male vs female       0.47 (0.11-1.99)*       0.304         BMI $\geq$ 30       1.75 (0.88-3.49)       0.111 $<30$ 0.96 (0.86-1.07)       0.449 $\geq$ 30 vs <30	Female $1.97 (0.47-8.25)$ $0.353$ $1.36 (0.67-2.76)$ Male vs female $0.47 (0.11-1.99)*$ $0.304$ $0.81 (0.38-1.72)*$ BMI $\geq 30$ $1.75 (0.88-3.49)$ $0.111$ $1.70 (0.94-3.07)$ $<30$ $0.96 (0.86-1.07)$ $0.449$ $1.14 (0.99-1.31)$ $\geq 30 vs < 30$ $1.82 (0.91-3.66)*$ $0.092$ $1.49 (0.81-2.74)*$ DiseaseHealthy $1.00 (0.85-1.17)$ $0.977$ $1.16 (1.01-1.33)$ statuesOther $1.02 (0.19-5.52)$ $0.982$ $-$ Follow- $\geq 6$ $0.96 (0.86-1.07)$ $0.449$ $1.14 (0.99-1.31)$ up $< 6$ $1.75 (0.88-3.49)$ $0.111$ $1.74 (0.87-3.49)$ duration $\geq 6 vs < 6$ $0.55 (0.27-1.10)*$ $0.092$ $0.66 (0.32-1.33)*$ BMI, body mass index; CI: confidence interval; OSA, obst relative risk. * Reported as ratio of RR and 95% CI.OSA and CHD riskThe pooled data of meta-analysis showed that mild OSA the risk of CHD (RR: $1.25$ ; $95\%$ CI: $0.95-1.66$ ; $P = 0.117$ ; T2), whereas moderate OSA (RR: $1.38$ ; $95\%$ CI: $1.04-1.83$ ;	Female $1.97 (0.47 - 8.25)$ $0.353$ $1.36 (0.67 - 2.76)$ $0.399$ Male vs female $0.47 (0.11 - 1.99)^*$ $0.304$ $0.81 (0.38 - 1.72)^*$ $0.581$ BMI $\geq 30$ $1.75 (0.88 - 3.49)$ $0.111$ $1.70 (0.94 - 3.07)$ $0.079$ $< 30$ $0.96 (0.86 - 1.07)$ $0.449$ $1.14 (0.99 - 1.31)$ $0.078$ $\geq 30 vs < 30$ $1.82 (0.91 - 3.66)^*$ $0.922$ $1.49 (0.81 - 2.74)^*$ $0.198$ DiseaseHealthy $1.00 (0.85 - 1.17)$ $0.977$ $1.16 (1.01 - 1.33)$ $0.034$ statuesOther $1.02 (0.19 - 5.52)$ $0.982$ $ -$ Healthy vs Other $0.98 (0.18 - 5.32)^*$ $0.982$ $ -$ Follow- $\geq 6$ $0.96 (0.86 - 1.07)$ $0.449$ $1.14 (0.99 - 1.31)$ $0.064$ up $< 6$ $1.75 (0.88 - 3.49)$ $0.111$ $1.74 (0.87 - 3.49)$ $0.120$ duration $\geq 6 vs < 6$ $0.55 (0.27 - 1.10)^*$ $0.092$ $0.66 (0.32 - 1.33)^*$ $0.242$ BMI, body mass index; CI: confidence interval; OSA, obstructive sleep relative risk. * Reported as ratio or RR and 95% CI.Dise and char of meta-analysis showed that mild OSA was not as the risk of CHD (RR: 1.25; 95% CI: $0.95 - 1.66; P = 0.117;$ Table 2 and 32Dise moderate OSA (RR: 1.38; 95% CI: $1.04 - 1.83; P = 0.026;$	Female       1.97 (0.47-8.25)       0.353       1.36 (0.67-2.76)       0.399       1.98 (0.64-6.06)         Male vs female       0.47 (0.11-1.99)*       0.304       0.81 (0.38-1.72)*       0.581       0.91 (0.27-3.08)*         BMI       230       1.75 (0.88-3.49)       0.111       1.70 (0.94-3.07)       0.079       2.72 (1.80-4.10)         <30

## **OSA** and CHD risk

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Table 4. Gender difference for other outcomes

Page	e 23 of 55			BMJ	l Open			вмЈ Ор	
1 2								en: first	
3 4		and Supplen	nental 2) were asso	ociated w	ith a significantly	increased ri	sk of CHD.	publist	
5 6 7		Stratified and	alyses according to	gender v	vere conducted for	different lev	vels of OSA	ned as	
8 9 10		versus norma	al group, and it was	found tha	t patients with seve	ere OSA had	significantly	10.1136 Prote	
11 12		increased the risk of CHD in men (RR: 1.65; 95% CI: 1.06–2.57; $P = 0.027$ ). No other							
13 14 15		significant differences were detected (Table 4).							
16 17 18			Table 4. Ge	ender diffe	erence for other out	comes		BMJ Open: first published as 10.1136/bmjopen-2016-013983 on 22 Protected by copyright, includin∉f ₽	
19 <sup>-</sup> 20 21	Outcome	Subgroup	Mild OSA (RR	<i>P</i> value	Moderate OSA	<i>P</i> value for	Severe OSA (RR	P velue 22	
22 23			with 95% CI)	for mild	(RR with 95% CI)	moderate	with 95% CI)	for uses rel	
24 25 26				OSA		OSA		er 2017. signeme related t	
27 - 28 29 30	CHD	Men	0.93 (0.72–1.21)	0.596	1.09 (0.80–1.48)	0.582	1.65 (1.06–2.57)	bownloaded nt Superieur o te& and da	
31 32 33		Women	1.92 (0.43-8.64)	0.394	1.51 (0.38–5.97)	0.559	1.10 (0.12–9.87)	d data mi	
34 35 36		Men vs women	0.48 (0.11–2.22)*	0.351	0.72 (0.18–2.96)*	0.651	1.50 (0.16–14.22)*	0.7 <b>9</b> 4 0.7 <b>9</b> 4 0.7 <b>9</b> 4	
37 38 39	Stroke	Men	1.86 (0.67–5.14)	0.232	1.86 (0.70–4.95)	0.214	2.86 (1.10-7.41)	0.294 Al traieng, and similar technologies 0.595 0.00 0.00 0.00 0.00 0.00 0.00 0.0	
40 41 42		Women	1.34 (0.76–2.36)	0.311	1.20 (0.67–2.15)	0.542	1.21 (0.65–2.25)	and 0.555 mi	
43 44 45		Men vs women	1.39 (0.43–4.45)*	0.581	1.55 (0.50-4.84)*	0.451	2.36 (0.76–7.38)*	llar techn	
46 47 48	Cardiac	Men	_	_	1.15 (0.41–3.23)	0.791	2.87 (1.13-7.27)	14, 2025 10lo∰es. 0	
49 50 51 52	death	Women	_	_	0.94 (0.19–4.61)	0.939	3.71 (0.41–33.87)	0.245 <b>Agen</b>	
53 54 55 56 57 58		Men vs women	_	_	1.22 (0.18-8.17)*	0.935	0.77 (0.07–8.49)*	0.245 Al traiting, and similar technologies. 0.245 0.834 0.834	
59 60								) de l	

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All-cause	Men	_	_	_	-	1.72 (1.22–2.43)	0.002 lish	
mortality	Women	-	_	-	_	3.50 (1.23–9.97)	0.019 as P	
)	Men vs women	-	_	_	-	0.49 (0.16–1.48)*	as 10.1136/bmjopen-2016-013983 on 22 0.0 Protected by Sopyright including 1 0.559 0.5500 0.550 0.5500 0.550 0.5500	
Heart failure	Men	0.88 (0.57–1.35)	0.561	1.13 (0.68–1.88)	0.639	1.58 (0.93–2.67)	реп-201 0.® 0.руг	
, , ,	Women	1.13 (0.80–1.60)	0.493	1.01 (0.60–1.70)	0.970	1.19 (0.56–2.52)	6-013983 0.69 incl	
	Men vs women	0.78 (0.45–1.35)*	0.376	1.12 (0.54–2.32)*	0.762	1.33 (0.53–3.33)*	0.545 ud 22 D	
	CHD, coron	ary heart disease; (	OSA, obst	tructive sleep apnea	. * Reporte	ed as ratio of	ecemt Ens r uses	
	RR and 95% CI.							
6 7 OSA and stroke risk							December 2017. Downloaded Enseignement Superieur for uses related to text and da	
	CI: 0.69–2.41; $P = 0.424$ ; Table 2 and Supplemental 2) and moderate OSA (RR: 1.35;							
severe OSA was associated with an increased risk of stroke (RR: 2.15; 95% CI:						open. aining		
95% CI: $0.82-2.23$ , $P = 0.243$ , Table 2 and Supplemental 2) and stroke, whereas severe OSA was associated with an increased risk of stroke (RR: 2.15; 95% CI: 1.42-3.24; $P < 0.001$ ; Table 2 and Supplemental 2). Subgroup analysis on the basis of gender indicated that severe OSA had a harmful effect on the risk of stroke in men (RR: 2.86; 95% CI: $1.10-7.41$ ; $P = 0.031$ ; Table 4).							, and	
							om/ on similar t	
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	OSA and cardiac death risk The summary RRs showed that mild OSA (RR: 1.80; 95% CI: 0.68–4.76; P = 0.236; Table 2 and Supplemental 2) and moderate OSA (RR: 1.11; 95% CI: 0.53–2.35;							
	<i>P</i> = 0.781; 1	Cable 2 and Suppler	mental 2)	were not associated	with cardia	ac death risk,	://bmjopen.bmj.com/ on June 14, 2025 at Agence Bibliographique de l , Al training, and similar technologies.	
	Farrier		(1)				-	

#### **OSA** and stroke risk

#### **OSA** and cardiac death risk

whereas severe OSA significantly increased the risk of cardiac death (RR: 2.96; 95% CI: 1.45–6.01; P = 0.003; Table 2 and Supplemental 2). Subgroup analysis showed that severe OSA was associated with an increased risk of cardiac death in men (RR: 2.87; 95% CI: 1.13–7.27; P = 0.026; Table 4).

#### **OSA** and all-cause mortality risk

No significant association was found between mild OSA (RR: 1.26; 95% CI: 0.77–2.07; P = 0.354; Table 2 and Supplemental 2), moderate OSA (RR: 1.04; 95% CI: 0.60–1.79; P = 0.895; Table 2 and Supplemental 2), and all-cause mortality risk. However, severe OSA had a harmful impact on the all-cause mortality (RR: 1.54; 95% CI: 1.21–1.97; P < 0.001; Table 2 and Supplemental 2). Stratified analysis suggested that severe OSA increased the risk of all-cause mortality in men (RR: 1.72; 95% CI: 1.22–2.43; P = 0.002) and women (RR: 3.50; 95% CI: 1.23–9.97; P = 0.019; Table 4).

#### **OSA** and heart failure risk

The summary results indicated no significant differences between mild OSA (RR: 1.02; 95% CI: 0.78–1.34; P = 0.868), moderate OSA (RR: 1.07; 95% CI: 0.74–1.54; P = 0.719), and severe OSA (RR: 1.44; 95% CI: 0.94–2.21; P = 0.097), and the risk of heart failure (Table 2 and Supplemental 2). Subgroup analysis reported similar results compared with the overall analysis (Table 4).

#### **Publication bias**

Review of the funnel plots could not rule out the potential publication bias for

MACEs (Fig. 5). The Egger and Begg test results showed no evidence of publication bias for MACEs of mild OSA (*P* value for Egger: 0.132; *P* value for Begg: 0.221) and moderate OSA (*P* value for Egger: 0.052; *P* value for Begg: 0.452). Although the Begg test showed no evidence of publication bias for MACEs of severe OSA (*P* = 0.118), the Egger test showed potential evidence of publication bias for MACEs of severe OSA (*P* < 0.001). The conclusion did not change after adjustment for publication bias using the trim-and-fill method [37].

#### Discussion

The present study was based on prospective cohort studies and explored all possible correlations between OSA and the outcomes of MACEs, CHD, stroke, cardiac death, all-cause mortality, and heart failure. This large quantitative study included 24,308 individuals from 16 prospective cohort studies with a broad range of populations. The findings from the present meta-analysis suggested that mild OSA had no significant impact on the risk of vascular outcomes and all-cause mortality, moderate OSA was associated with an increased risk of MACEs and CHD, and severe OSA had a harmful effect on the risk of MACEs, CHD, stroke, cardiac death, and all-cause mortality.

A previous meta-analysis suggested that OSA was associated with stroke, but its relationship with ischemic heart disease and cardiovascular mortality needs further research [38]. However, this study could not illustrate the impact of different levels of OSA on the risk of serious cardiovascular outcomes. Further, Dong et al. suggested that moderate-to-severe OSA significantly increased the risk of cardiovascular

diseases, in particular, the risk of stroke [39]. Similarly, Ge et al. indicated that severe OSA is a strong independent predictor of cardiovascular and all-cause mortality. CPAP treatment was associated with decreased cardiovascular mortality [40]. However, these two studies could not evaluate the association of OSA with the risk of vascular outcomes and all-cause mortality in specific subpopulations. In addition, Wang et al. suggested that severe OSA significantly increased the risk of CHD and stroke, and all-cause mortality. A positive association with CHD was observed for moderate OSA but not for mild OSA [41]. However, whether this relationship differs according to the characteristics of participants remains unclear. Finally, Xie et al. conducted a meta-analysis to evaluate the relationship between OSA and recurrent vascular events and all-cause mortality [42]. However, they just compared the highest AHI versus lowest AHI, whereas the degree of OSA and subsequent adverse outcomes were not available. Therefore, a comprehensive meta-analysis of these prospective cohort studies was performed to evaluate any possible correlates between OSA and vascular outcomes.

3MJ Open: first published as 10.1136/bmjopen-2016-013983 on 22 December 2017. Downloaded from http://bmjopen.bmj.com/ on June 14, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

No significant difference was observed between mild OSA and the risk of vascular outcomes. However, several studies included in this study reported inconsistent results. Young et al. suggested that mild OSA significantly increased the risk of CHD by 92% [25], whereas Punjabi et al. indicated that mild OSA might have a harmful effect on the risk of CHD [28]. This might be because these two studies used healthy individuals as controls, which may make them more susceptible to acquired significant conclusion. Furthermore, most of these studies did not take into account

potential confounders for the risk of cardiovascular disease. Moderate-to-severe OSA might play an important role in the risk of vascular outcomes. Shah et al. concluded that OSA increased the risk of coronary events or death from cardiovascular causes [29]. Nearly all included studies reported adverse outcomes for severe OSA. Finally, Previous studies indicated that OSA was a cause of diabetes, which was an independent risk factor for MACEs [43].

Subgroup analyses reported similar conclusions. Gender might have an impact on the relationship between OSA and CHD, stroke, or cardiac death, although the sex difference was not statistically significant. The possible reasons could be the lower prevalence of severe OSA in women and the later age of onset of OSA in women than in men. Furthermore, OSA in women always occurred after menopause. Physiological response to OSA is another reason for this nonsignificant difference. Finally, these conclusions might be unreliable because smaller cohorts were included in each subset. Therefore, further large-scale studies were needed to verify this difference. Therefore, a relative result was given, and a synthetic and comprehensive review was provided.

No significant difference was found between mild or moderate OSA and all-cause mortality, while severe OSA was associated with an increased risk of all-cause mortality. Further, these significant associations were also observed in men and women separately. Although the effect estimate in women was larger than that in men, no gender difference was found in the relationship between OSA and all-cause mortality. This might be because the number of studies that reported the relationship between severe OSA and all-cause mortality was smaller than expected, and a broad

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95% CI was acquired. Therefore, the association of severe OSA with all-cause mortality in women was variable and should be verified in future large-scale prospective studies.

Three strengths of this study should be highlighted. First, only prospective studies were included, which eliminated selection and recall bias, and could be of concern in retrospective case-control studies. Second, the large sample size allowed us to quantitatively assess the association of OSA with the risk of vascular outcomes and mortality, and thus the findings were potentially more robust than those of any individual study. Third, the summary RRs were calculated to evaluate any potential difference between subsets according to the characteristics of participants.

The limitations of this study were as follows: (1) the adjusted models were different across the included studies, and these factors might have played an important role in developing vascular outcomes; (2) in a meta-analysis of published studies, publication bias was an inevitable problem; and (3) the analysis used pooled data (individual data were not available), which restricted performing a more detailed relevant analysis and obtaining more comprehensive results. 3MJ Open: first published as 10.1136/bmjopen-2016-013983 on 22 December 2017. Downloaded from http://bmjopen.bmj.com/ on June 14, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

The results of this study suggested that moderate-to-severe OSA might play an important role in the risk of vascular outcomes, especially for men. Future studies should focus on specific populations to analyze the gender difference to study the association between OSA and vascular outcomes.

## **Author Contributions**

Chengjuan Xie carried out the studies, participated in collecting data, and drafted the manuscript. Ruolin Zhu performed the statistical analysis and participated in its design. Yanghua Tian and Kai Wang helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of interests: All authors declare no conflict of interest.

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Data sharing statement: No additional data available.

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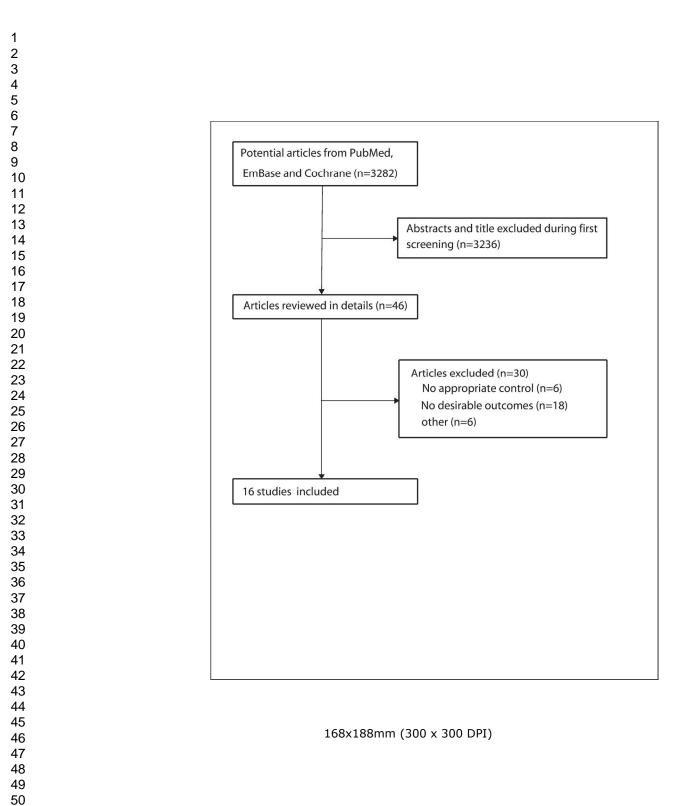
## **Figure legends:**

- Figure 1. Study-selection process.
- Figure 2. Association between mild OSA and MACEs.
- Figure 3. Association between moderate OSA and MACEs.
- Figure 4. Association between severe OSA and MACEs.

Figure 5. Funnel plots.

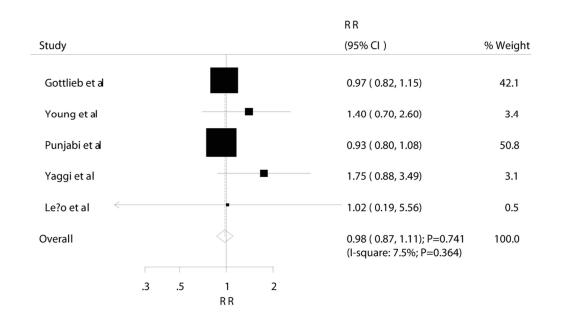
## Supplemental legends:

ecklist Checklist S1. MOOSE Checklist.



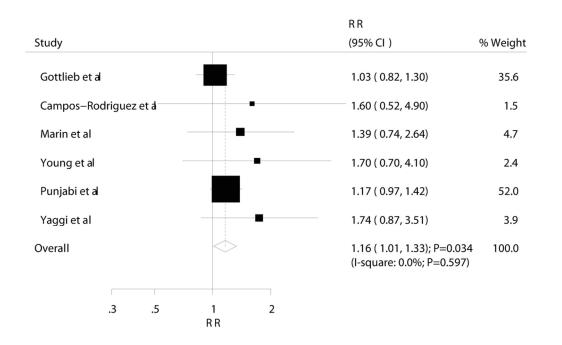
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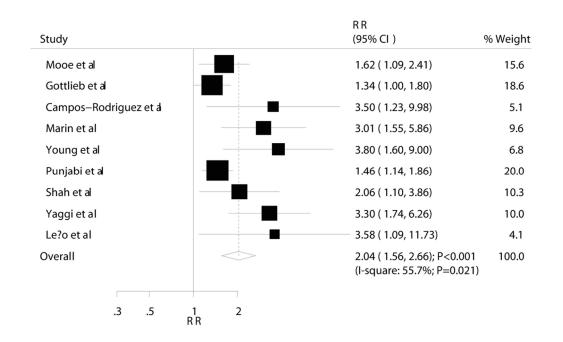
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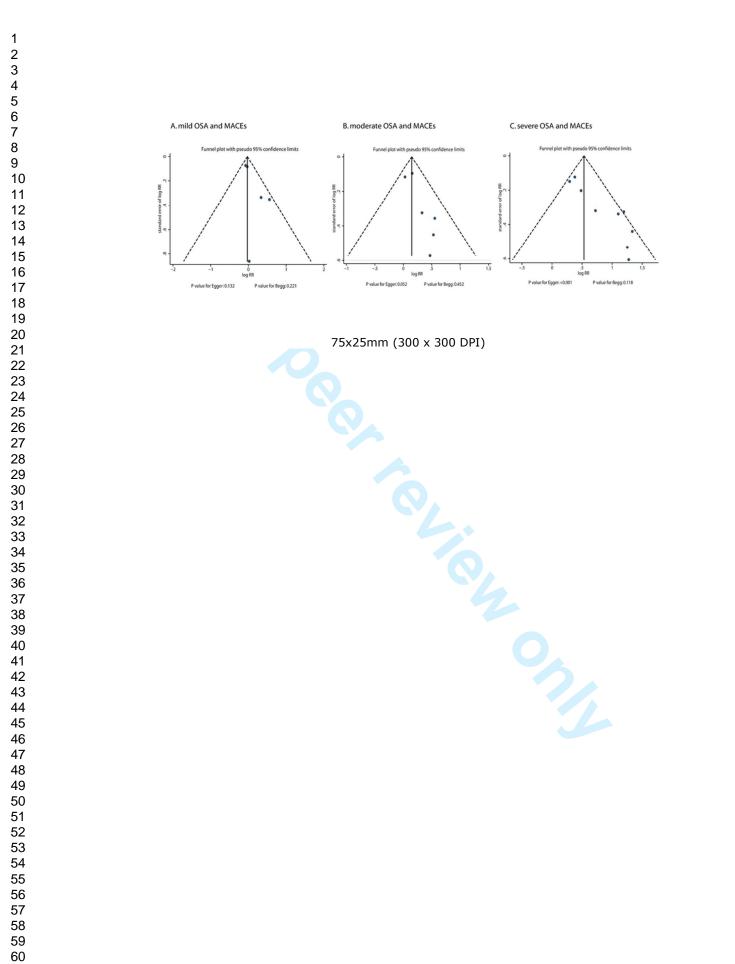
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Title:	
	Search strategy
#1	"Sleep Apnea, Obstructive" [Mesh] OR "OSA" [All fields] OR "OHS" [All fields]
#2	Apneas, Obstructive Sleep OR Obstructive Sleep Apneas OR Sleep Apneas, Obstructive OR Obstructive Sleep Apnea Syndrome OR Obstructive Sleep Apnea OR OSAHS OR Syndrome, Sleep Apnea, Obstructive OR Sleep Apnea Syndrome, Obstructive OR Apnea, Obstructive Sleep OR Sleep Apnea Hypopnea Syndrome OR Syndrome, Obstructive Sleep Apnea OR Upper Airway Resistance Sleep Apnea Syndrome OR Syndrome, Upper Airway Resistance, Sleep Apnea OR Hypoventilation Syndrome, Obesity OR Syndrome, Obesity Hypoventilation OR Pickwickian Syndrome OR Syndrome, Pickwickian OR Obesity-Hypoventilation Syndrome
#3	"Sleep Apnea Syndromes" [Mesh] OR "SAS" [All fields]
#4	Apnea Syndrome, Sleep OR Apnea Syndromes, Sleep OR Sleep Apnea Syndrome OR Apnea, Sleep OR Apneas, Sleep OR Sleep Apnea OR Sleep Apneas OR Sleep Hypopnea OR Hypopnea, Sleep OR Hypopneas, Sleep OR Sleep Hypopneas OR Sleep-Disordered Breathing OR Breathing, Sleep-Disordered OR Sleep Disordered Breathing OR Sleep Apnea, Mixed Central and Obstructive OR Mixed Central and Obstructive Sleep Apnea OR Sleep Apnea, Mixed OR Mixed Sleep Apnea OR Mixed Sleep Apneas OR Sleep Apneas, Mixed OR Hypersomnia with Periodic Respiration
#5	"Sleep Apnea, Central" [Mesh] OR "CSA" [All fields]
#6	Apneas, Central Sleep OR Central Sleep Apneas OR Sleep Apneas, Central OR Apnea, Central OR Apneas, Central OR Central Apnea OR Central Apneas OR Apnea, Central Sleep OR Apnea, Sleep, Central OR Sleep Apnea, Lethal Central OR Central Sleep Apnea OR Central Sleep Apnea Syndrome OR Central Sleep Disordered Breathing OR Hypoventilation, Central Alveolar OR Alveolar Hypoventilation, Central OR Alveolar Hypoventilations, Central OR Central Alveolar Hypoventilation OR Hypoventilations, Central OR Central Sleep-Disordered Breathing, Central OR Breathing, Central Sleep-Disordered OR Breathings, Central OR Breathing, Central Sleep-Disordered OR Breathings, Central Sleep-Disordered OR Central Sleep-Disordered Breathing OR Central Sleep-Disordered Breathings, Central Sleep-Disordered Breathing OR Sleep-Disordered Breathings, Central Sleep-Disordered Breathing OR Sleep-Disordered Breathings, Central OR Central Alveolar Hypoventilation Syndrome OR Central Sleep Disordered Breathing, Central OR Sleep-Disordered Breathings, Central OR Central Alveolar Hypoventilation Syndrome OR Central Sleep Apnea, Secondary OR Secondary Central Sleep Apnea OR Sleep Apnea, Newborn, Primary OR Primary Sleep Apneas of Newborn OR Newborn Primary Sleep Apneas OR Central Sleep Apnea, Primary OR Primary Central Sleep Apnea
#7	"Continuous Positive Airway Pressure" [Mesh] OR "CPAP" [All fields] OR
#8	"Continuous Positive Airway Pressure/therapy" [Mesh] CPAP Ventilation OR Ventilation, CPAP OR Biphasic Continuous Positive Airway Pressure OR Bilevel Continuous Positive Airway Pressure OR Nasal Continuous Positive Airway Pressure OR nCPAP Ventilation OR Ventilation, nCPAP OR Airway Pressure Release Ventilation OR APRV Ventilation Mode OR APRV Ventilation Modes OR Ventilation Mode, APRV OR Ventilation Modes, APRV

#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	"Cardiovascular System" [Mesh]
#11	"Death" [Mesh] OR Determination of Death OR Near-Death Experience OR
	Cardiac Death OR Death, Cardiac OR "Mortality" [Mesh] OR "mortality" [All
	fields] OR "Disease" [Mesh] OR "disease*"
#12	#10 AND #11
#13	"Cardiovascular Diseases" [Mesh] OR "CVD" OR Cardiovascular Disease OR
	Disease, Cardiovascular OR Diseases, Cardiovascular
#14	"Myocardial Infarction" [Mesh] OR "MI" OR Infarction, Myocardial OR
	Infarctions, Myocardial OR Myocardial Infarctions OR Cardiovascular Stroke OR
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	Heart Attack OR Heart Attacks OR Myocardial Infarct OR Infarct, Myocardial OR
	Infarcts, Myocardial OR Myocardial Infarcts
#15	"Angina Pectoris" [Mesh] OR "Angina, Stable" [Mesh] OR "Microvascular
	Angina" [Mesh] OR "Angina, Unstable" [Mesh] OR Stenocardia OR Stenocardias
	OR Angor Pectoris OR "angina" [All fields] OR "Coronary Artery Disease" [Mesh] OR "CAD" OR "ischemic heart disease" [All fields] OR "Heart Failure" [Mesh]
	OR "Heart Failure, Diastolic" [Mesh] OR "Heart Failure, Systolic" [Mesh]
#16	"Cerebrovascular Disorders" [Mesh] OR "cerebrovascular" [All fields] OR
π10	"stroke*"
#17	"Death" [Mesh] OR Determination of Death OR Near-Death Experience OR
	Cardiac Death OR Death, Cardiac OR "Mortality" [Mesh] OR "mortality" [All
	fields] OR "mortality*"
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	"Prospective Studies" [Mesh] OR "Cohort Studies" [Mesh] OR "Follow-Up
	Studies" [Mesh] OR "prospective study" OR "cohort study" OR "follow-up study"
#20	#9 AND #18 AND #19

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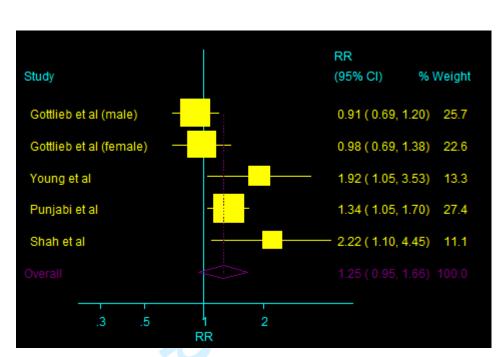


Figure S1. Association between mild OSA and CHD.

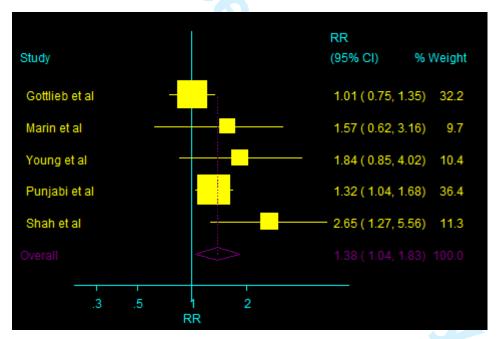


Figure S2. Association between moderate OSA and CHD.

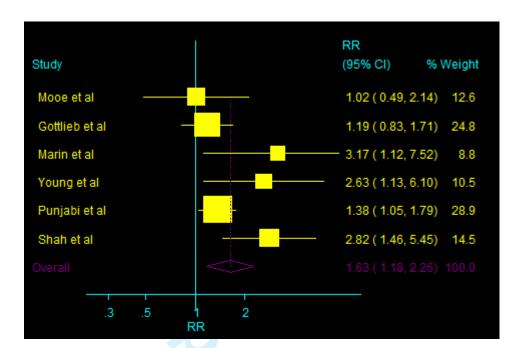
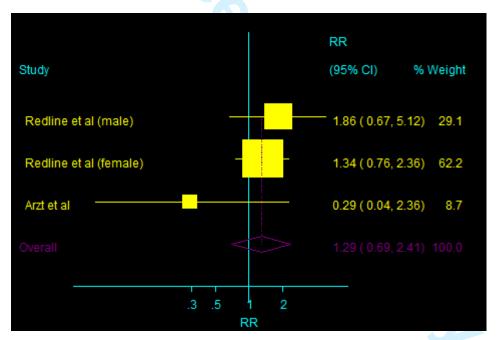
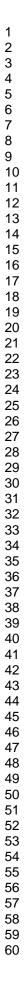


Figure S3. Association between severe OSA and CHD.



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Figure S4. Association between mild OSA and stroke.



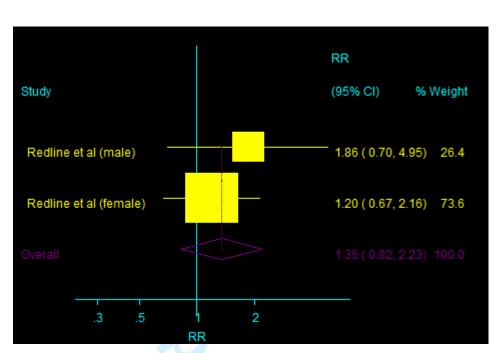


Figure S5. Association between moderate OSA and stroke.

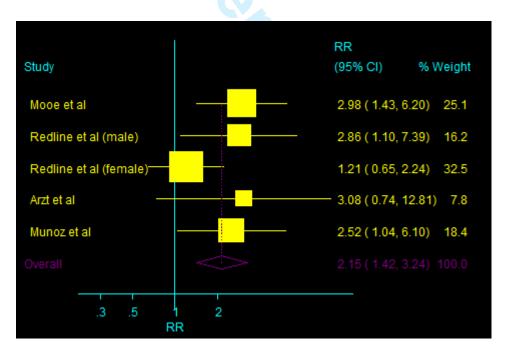


Figure S6. Association between severe OSA and stroke

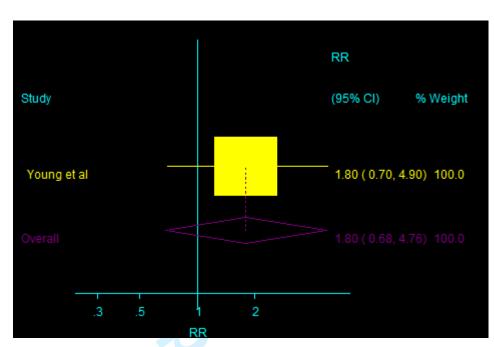
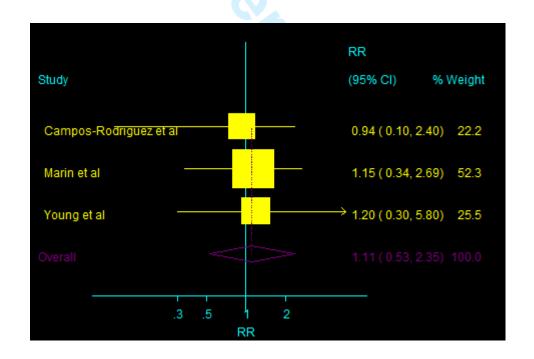
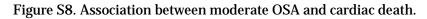
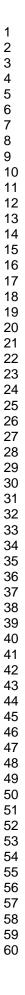


Figure S7. Association between mild OSA and cardiac death.





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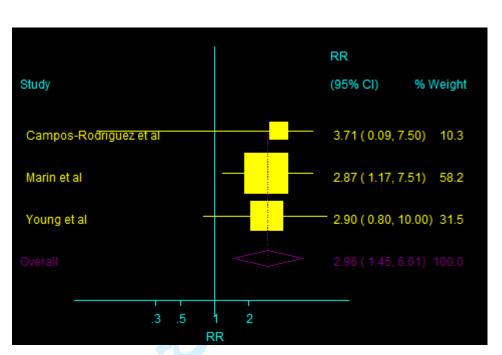


Figure S9. Association between severe OSA and cardiac death.

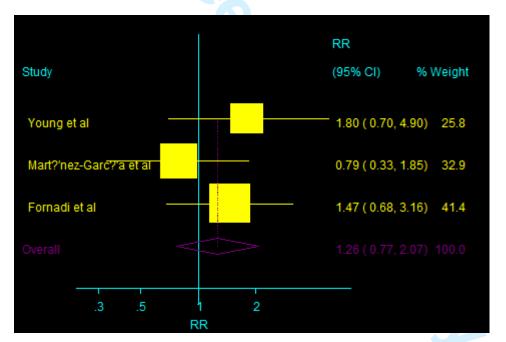


Figure S10. Association between mild OSA and all-cause death.

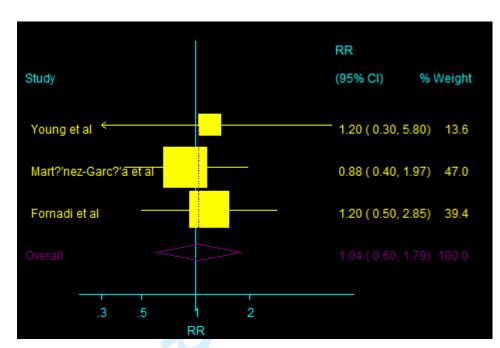


Figure S11. Association between moderate OSA and all-cause death.

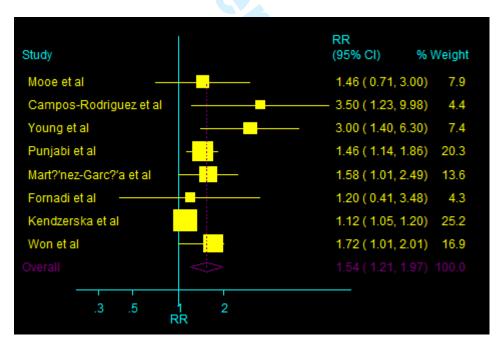


Figure S12. Association between severe OSA and all-cause death.

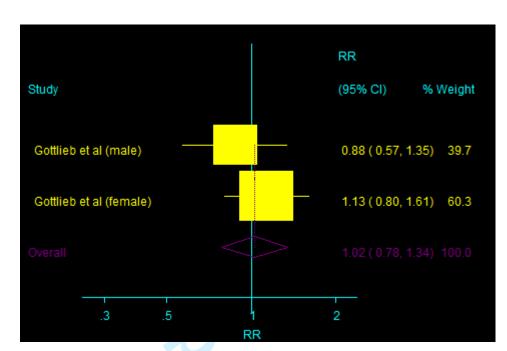


Figure S13. Association between mild OSA and heart failure.

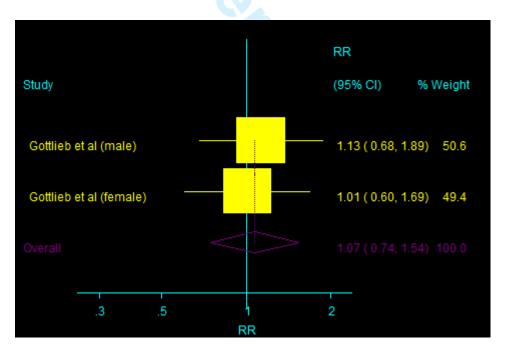


Figure S14. Association between moderate OSA and heart failure.

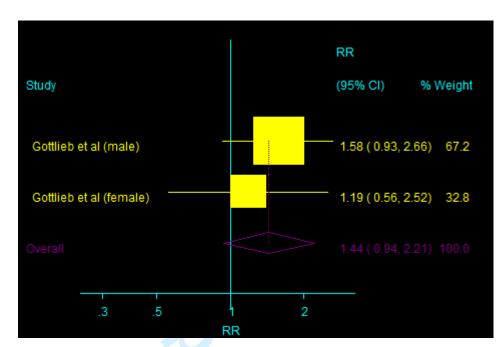


Figure S15. Association between severe OSA and heart failure.

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# MOOSE Statement: Reporting Checklist for Authors, Editors, and Reviewers of Meta-

Reporting Criteria	Reported (Yes/No)	Reported on Page
Reporting of background should include		
Problem definition	Yes	3
Hypothesis statement	Yes	3
Description of study outcomes	Yes	3
Type of exposure or intervention used	Yes	3 - 4
Type of study designs used	Yes	4
Study population	Yes	4
Reporting of search strategy should include		
Qualifications of searchers (e.g., librarians and investigators)	Yes	4 - 5
Search strategy, including time period used in the synthesis and key words	Yes	5
Effort to include all available studies, including contact with authors	Yes	5
Databases and registries searched	Yes	4–5
Search software used, name and version, including special features used	Yes	4–5
(e.g., explosion)		
Use of hand searching (e.g., reference lists of obtained articles)	Yes	5
List of citations located and those excluded, including justification	Yes	8
Method of addressing articles published in languages other than English	Yes	4
Method of handling abstracts and unpublished studies	Yes	4–5
Description of any contact with authors	No	NA
Reporting of methods should include		<u> </u>
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	No	5

Rationale for the selection and coding of data (e.g., sound clinical

Documentation of how data were classified and coded (e.g., multiple

Assessment of confounding (e.g., comparability of cases and controls in

Assessment of study quality, including blinding of quality assessors,

and stratification or regression on possible predictors of study results

principles or convenience)

studies where appropriate)

raters, blinding and inter-rater reliability)

For peer review only	/ - http://bmjopen.bm	j.com/site/about/guidelines.xhtml

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Assessment of heterogeneity	Yes	7
Description of statistical methods (e.g., complete description of fixed-	Yes	6–7
or random-effects models, justification of whether the chosen models		
account for predictors of study results, dose-response models, or		
cumulative meta-analysis) in sufficient detail to be replicated		
Provision of appropriate tables and graphics	Yes	6–7
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Yes	8
Table giving descriptive information for each study included	Yes	8-14
Results of sensitivity testing (e.g., subgroup analysis)	Yes	15–20
Indication of statistical uncertainty of findings	Yes	20
Reporting of discussion should include		
Quantitative assessment of bias (e.g., publication bias)	Yes	20
Justification for exclusion (e.g., exclusion of non-English language	No	21
citations)		
Assessment of quality of included studies	Yes	Table 1
Strengths and weaknesses	Yes	23
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	Yes	20–23
Generalization of the conclusions (e.g., appropriate for the data	Yes	23
presented and within the domain of the literature review)		
Guidelines for future research	Yes	23
Disclosure of funding source	Yes	24
NA, Not applicable.		