Research article

Impact of obstructive sleep apnea on aortic disease occurrence: A meta-analysis

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ABSTRACT

Objective: Aortic diseases, mainly including aortic dilatation, aortic aneurysm (AA) and aortic dissection (AD), have high morbidity and mortality. Many studies have suggested that obstructive sleep apnea (OSA) acts as a candidate risk factor for aortic diseases. Thus, we performed a meta-analysis to explore comprehensively the effect of OSA on the risk of aortic disease occurrence.

Methods: We searched PubMed, Embase and Cochrane Library databases from inception to February 2022 to identify studies investigating the association between OSA and aortic diameter dilatation, the prevalence of OSA in individuals with or without AA/AD and the incidence of AA/AD in individuals with or without OSA. The Newcastle-Ottawa Scale (NOS) and the Agency for Healthcare Research and Quality (AHRQ) were respectively used to evaluate the quality of the included cohort and cross-sectional studies. A random or fixed effect model was used to generate pooled effects according to interstudy heterogeneity. Sensitivity analyses were performed to test the robustness of the results.

Results: We identified 10 observational publications with 214,127 participants in this meta-analysis. OSA was significantly associated with increased aortic diameter (WMD = 1.46, 95% CI, 1.10–1.83, p < 0.001). OSA prevalence was higher in patients with AA/AD compared to their counterparts without AA/AD (OR = 1.90, 95% CI, 1.30–2.76, p = 0.001). No significant difference in the incidence of AA/AD was observed in individuals with or without OSA (RR = 0.85, 95% CI, 0.62–1.16, p = 0.307). Sensitivity analyses did not modify these results.

Conclusions: This meta-analysis suggests that OSA is associated with aortic diameter dilatation but does not affect AA/AD occurrence.

1. Introduction

Aortic diseases, which mainly include aortic dilatation, aortic aneurysm (AA) and aortic dissection (AD), have high morbidity and mortality [1]. It is estimated that the overall prevalence of AA and AD is around 1%–3% in the general population, with up to 10% prevalence in old people [2]. The global AA death rate per 100,000 population has increased from 2.49 in 1990 to 2.78 in 2010 [3]. It represents the 17th leading cause of death in individuals aged more than 60 years in the USA from 1999 to 2020 [4]. The mortality rate of AD ranges from 13% [5] to 33% [6] in elder patients. Aortic diseases are highly complex and multifactorial diseases caused by both genetic and environmental factors. Like other cardiovascular diseases, well-established risk factors associated with aortic diseases mainly include older age, male sex, smoking, a family history, hyperlipidemia and hypertension [7, 8, 9, 10]. Despite the

improvement in risk factor management, the incidence of aortic diseases continues to increase. Therefore, it is critical to find novel risk factors for limiting the occurrence of this life-threatening disease.

Obstructive sleep apnea (OSA) is an increasingly prevalent sleep disorder characterized by recurrent partial or complete collapse of the upper airway during sleep, with consequent decrease in oxygen saturation and arousal which lead to poor sleep quality and excessive daytime sleepiness [11]. In western countries, 2%–4% of adult population suffer from symptomatic OSA [12], while at least 20% of males and 10% of females are asymptomatic [13]. Previous studies have reported that OSA was closely involved in the pathogenesis and progression of many cardiovascular disorders including hypertension, coronary artery disease, and stroke [14]. Notably, recent studies proposed a possible link between OSA and aortic diseases. Saruhara *et al.* [15] reported that patients with aortic diseases had higher incidences of moderate to severe OSA, and

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Table 1. Database search strategy.

Database	Search (February 13th 2022)
Pubmed	(("Sleep Apnea, Obstructive"[Mesh]) OR (((((((((((obstructive sleep apnea[Title/Abstract]) OR (obstructive sleep apnoea[Title/Abstract])) OR (OSA[Title/Abstract])) OR (sleep apnea[Title/Abstract])) OR (sleep apnoea[Title/Abstract])) OR (sleep disordered breathing[Title/Abstract])) OR (apnea syndrome[Title/Abstract])) OR (sleep apnea syndrome[Title/Abstract])) OR (obstructive sleep apnea syndrome[Title/Abstract])) OR (OSAHS[Title/Abstract]))) AND ((((((("Aortic Aneurysm, Abdominal"[Mesh]) OR (abdominal aortic aneurysm[Title/Abstract])) OR ("Aortic Aneurysm, Thoracic"[Mesh]) OR (thoracic aortic aneurysm[Title/Abstract])) OR (((((thoracoabdominal aortic aneurysm[Title/Abstract]) OR (aortic aneurysm[Title/Abstract])) OR (aneurysm[Title/Abstract])) OR (aortic[Title/Abstract])) OR (aorta[Title/Abstract]))) OR (("Aneurysm, Dissecting"[Mesh]) OR (((((dissecting aneurysm[Title/Abstract]) OR (dissection, blood vessel[Title/Abstract])) OR (blood vessel dissection[Title/Abstract])) OR (aortic dissection[Title/Abstract])) OR (dissection, aortic[Title/Abstract])))) OR ((((aortic dilation[Title/Abstract]) OR (aortic dilatation[Title/Abstract])) OR (aortic diameter[Title/Abstract])) OR (aortic root[Title/Abstract]))))
Embase	('obstructive sleep apnea':ti,ab,kw OR 'obstructive sleep apnoea':ti,ab,kw OR osa:ti,ab,kw OR 'sleep apnea':ti,ab,kw OR 'sleep apnoea':ti,ab,kw OR 'sleep disordered breathing':ti,ab,kw OR 'apnea syndrome':ti,ab,kw OR 'sleep apnea syndrome':ti,ab,kw OR 'obstructive sleep apnea syndrome':ti,ab,kw OR osahs:ti,ab,kw) AND (('abdominal aortic aneurysm':ti,ab,kw OR 'thoracic aortic aneurysm':ti,ab,kw OR 'thoracoabdominal aortic aneurysm':ti,ab,kw OR 'aortic aneurysm':ti,ab,kw OR aneurysm:ti,ab,kw OR aortic:ti,ab,kw OR aorta:ti,ab,kw) OR ('dissecting aneurysm':ti,ab,kw OR 'blood vessel dissection':ti,ab,kw OR 'aortic dissection':ti,ab,kw) OR ('aortic dilation':ti,ab,kw OR 'aortic dilatation':ti,ab,kw OR 'aortic diameter':ti,ab,kw OR 'aortic root':ti,ab,kw))
Cochrane	(((sleep disordered breathing):ti,ab,kw OR (apnea syndrome):ti,ab,kw OR (sleep apnea syndrome):ti,ab,kw OR (obstructive sleep apnea syndrome):ti,ab,kw OR (OSAHS):ti,ab,kw) OR((obstructive sleep apnea):ti,ab,kw OR (obstructive sleep apnoea):ti,ab,kw OR (OSA):ti,ab,kw OR (sleep apnea):ti,ab,kw OR (sleep apnoea):ti,ab,kw) OR (MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees)) AND (((MeSH descriptor: [Aortic Aneurysm, Abdominal] explode all trees) OR (MeSH descriptor: [Aortic Aneurysm, Thoracic] explode all trees) OR ((abdominal aortic aneurysm):ti,ab,kw OR (thoracic aortic aneurysm):ti,ab,kw OR (thoracoabdominal aortic aneurysm):ti,ab,kw OR (aortic aneurysm):ti,ab,kw OR (aneurysm):ti,ab,kw) OR((aortic):ti,ab,kw OR (aorta):ti,ab,kw)) OR ((MeSH descriptor: [Aneurysm, Dissecting] explode all trees)OR((dissecting aneurysm):ti,ab,kw OR (dissection, blood vessel):ti,ab,kw OR (blood vessel dissection):ti,ab,kw OR (aortic dissection):ti,ab,kw OR (dissection, aortic):ti,ab,kw)) OR ((aortic dilation):ti,ab,kw OR (aortic dilatation):ti,ab,kw OR (aortic diameter):ti,ab,kw OR (aortic root):ti,ab,kw))

recommended that screening for OSA may be helpful for early detection of patients with aortic diseases. Stöwhas *et al.* [16] found that simulated obstructive hypopnea was associated with an acute increase in proximal aortic diameter in healthy humans. In animal experiments, an increase in aortic diameters was observed during obstructive apnea episodes [17, 18]. At present, several pathomechanisms by which OSA exerts its adverse impact on aortic structure have been proposed, such as increased transmural aortic pressure [19], sympathetic drive and subsequent hypertension [20, 21], increased oxidative stress and inflammation [22, 23]. All of these studies identify OSA as a candidate risk factor for aortic disease occurrence.

Based on the high mortality of aortic diseases and many evidences suggesting its incidence might be related to OSA, it is essential to determine the effect of OSA on aortic disease incidence. Thus, this meta-analysis of observational studies attempts to explore comprehensively a potential relationship between OSA and aortic disease occurrence, and to provide new lights on the development and prevention of aortic diseases.

2. Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. The study was not preregistered with any database and no study protocol was available.

2.1. Search strategy

PubMed, Embase and Cochrane Library databases were systematically searched from inception to February 2022 to identify studies which accessed the association between OSA and aortic diseases (including aortic dilatation, AA and AD). The search was conducted using a combination of Medical Subject Heading (MeSH) or free-text search terms related to the OSA (ie, "obstructive sleep apnea", "OSAS" and so on) and aortic diseases (ie, "aortic dilatation", "aortic aneurysm", "aortic dissection" and so on). The detailed search strategy of databases is presented in Table 1. Reference lists of relevant publications were hand searched for additional studies.

2.2. Study selection

The criteria for inclusion of the meta-analysis were as follows:
(1) case-control studies, prospective or retrospective cohort studies and cross-sectional studies; (2) studies investigating the relationships between OSA and aortic diseases, including I) studies reporting the prevalence of OSA in participants with or without aortic diseases; II) studies reporting the incidence of aortic events (AA and AD) or aortic diameter in participants with or without OSA; (3) studies in which the diagnosis of OSA was based on polysomnography (PSG) or respiratory polygraphy or a recognized definition; (4) studies in which the measurement of aortic diameter was based on the echocardiography or computed tomography or magnetic resonance imaging (MRI); (5) studies published in English.

Criteria for exclusion were as follows:
(1) congress abstracts, case reports, reviews, editorials, letters, systematic reviews, meta-analyses; (2) studies investigating aortic stiffness, Marfan's syndrome, connective tissue disorders; (3) patients with other sleep disorders, such as central sleep apnea; (4) patients who received or are receiving OSA treatment; (5) animal or *in vitro* experiments; (6) studies which were conducted on child or adolescent.

2.3. Data extraction

Two investigators (TZ and BL) independently reviewed all relevant studies, screened eligible literatures according to the inclusion and exclusion criteria and extracted data from eligible studies. Any disagreement was resolved by discussion and consensus with a third investigator (YW).

The information of the extracted data included the following: study design, authors, published year, country, characteristics of the patients (number, age, men proportion, BMI and blood pressure), OSA definition, OSA prevalence, AA/AD incidence and diagnostic methods.

2.4. Quality assessment

The methodological quality of the included studies and the risk of bias were assessed independently by two authors (TZ and BL). The discrepancies were eliminated by discussion and consensus with another author (YW).

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included cohort and case-control studies. This scale uses a star system (with a maximum of 9 stars) to access the quality based on (1) selection of participants; (2) comparability of study groups; and (3) ascertainment of outcomes of interest. Studies that scored 0–3, 4–6, 7–9 stars were considered of low, moderate and high quality respectively.

The Agency for Healthcare Research and Quality (AHRQ) which consists of eleven items was used to judge the quality of the cross-sectional studies. An individual item was scored '1' if it was answered

'Yes', otherwise the item was scored '0'. Scores of 0–3, 4–7 and 8–11 were categorized as low, moderate and high quality respectively.

2.5. Statistical analysis

All statistical analyses were performed with the Stata12.0 software (Stata Corp, College Station, TX, USA). The pooled odds ratio (OR) with 95% confidence interval (CI) was calculated to assess the association between OSA and AA/AD in cross-sectional and case-control studies, while the risk ratio (RR) or hazard ratio (HR) with 95% CI was pooled in longitudinal cohort studies. Weighted mean difference (WMD) with 95% CI was used to determine the difference of aortic diameter between OSA patients and controls. I^2 statistic was used to assess heterogeneity across the involved studies. $I^2 > 50\%$ indicated significant heterogeneity between studies, the random effect model was used to generate pooled effects. Otherwise, the fixed effect model was employed. Sensitivity analyses were performed using a leave-one-out strategy to test the robustness of the results.

3. Results

3.1. Literature search

1189 citations from PubMed, Embase and Cochrane Library databases and 11 publications yielded by manually searching the references of relevant studies were identified in the initial search. 73 publications

underwent further full-text screening after reviewing titles and abstracts. Of these, 10 publications with 11 studies met the inclusion criteria and were enrolled in this meta-analysis (Figure 1).

3.2. Characteristics and quality of included studies

Table 2 outlines the characteristics of the included studies. All the eligible studies had an observational (cross-sectional or cohort) design. Seven of the studies were cross-sectional studies [24, 25, 26, 27, 28, 29, 30], 2 were cohort studies [31, 32], and 1 publication reported both a cross-sectional data and a prospective cohort [33]. A total of 214,127 participants were included in this meta-analysis in which most studies had a higher proportion of male participants. Table 3 and Table 4 respectively show the outcomes of included studies investigating the association between OSA and aortic dilatation or AA/AD. Among the included studies, 3 studies with 548 participants accessed the OSA prevalence in participants with or without AA or AD [29, 30, 33], 3 studies with 212,160 participants accessed the AA or AD incidence in participants with or without OSA [31, 32, 33], and 5 studies with 1419 participants reported the aortic diameter in participants with or without OSA [24, 25, 26, 27, 28]. Eight studies were carried out in Asia (China and Singapore) [24, 25, 26, 27, 31, 32, 33], 2 studies were carried out in Europe (Spain and Switzerland) [29, 30] and 1 study was done in USA [28]. Polysomnography or respiratory polygraphy was performed to define OSA in most of studies except that 2 studies [31, 32] used ICD codes. Aortic root diameter or ascending aortic diameter was measured
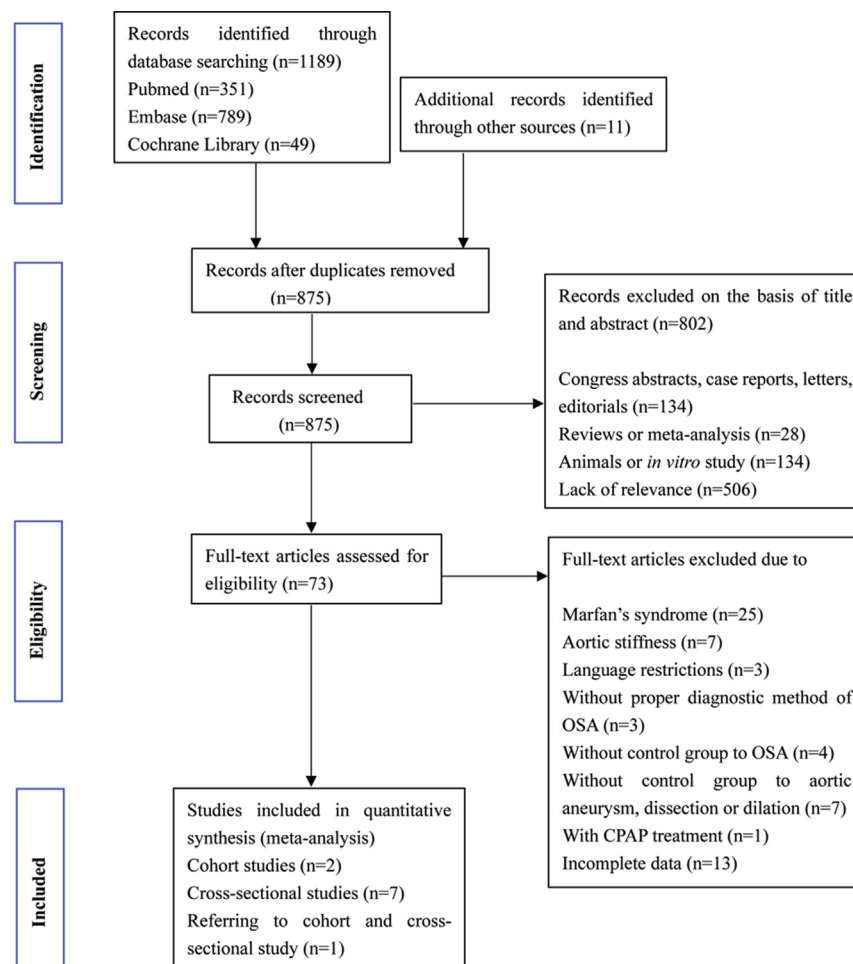

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of study selection. OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure.

Table 2. Characteristics of the included studies.

Study typ	Author	Year	Country	Sample size (n)/male (%)	Age (years)	BMI (kg/m²)	BP (mmHg)	
							Systolic blood pressure	Diastolic blood pressure
Cross-sectional	Chen [24]	2014	China	Sample size (n)/male (%)	OSA 49 ± 10 Control 47 ± 8	OSA 26.9 ± 3.6 Control 24.1 ± 3.4	OSA 139 ± 16 Control 133 ± 19	OSA 79 ± 11 Control 80 ± 13
	Lee [25]	2010	Singapore	OSA 64 (100) Control 30 (100)	OSA 54 ± 10 Control 50 ± 9	OSA 24.9 ± 3 Control 24.0 ± 3	OSA 117 ± 19 Control 108 ± 12	OSA 71 ± 11 Control 65 ± 8
	Hong [27]	2021	China	Moderate-to-severe OSA 188 (86) Mild OSA 86 (69) Control 78 (64)	Moderate-to-severe OSA 47.1 ± 10.3 Mild OSA 49.2 ± 14.0 Control 47.0 ± 12.3	Moderate-to-severe OSA 27.1 ± 3.8 Mild OSA 25.4 ± 3.7 Control 23.9 ± 3.2	NA	NA
	Kwon [28]	2019	USA	Significant OSA 406 (53.5) Mild OSA 215 (34.0) Control 87 (25.3)	Significant OSA 68.5 ± 8.9 Mild OSA 67.1 ± 8.8 Control 65.5 ± 8.6	NA	Significant OSA 129 ± 17 Mild OSA 126 ± 17 Control 121 ± 18	NA
	Sun [26]	2014	China	OSA 136 (65.4) Control 50 (74)	OSA 63.3 ± 10.6 Control 62.2 ± 10.8	OSA 30.94 ± 4.15 Control 29.66 ± 4.42	OSA 136 ± 16 Control 122 ± 14	OSA 89 ± 11 Control 83 ± 10
	Gaisl [29]	2020	Switzerland	TAA 208 (81.7) Control 104 (81.7)	TAA 65.94 ± 10.49 Control 64.43 ± 11.74	TAA 26.89 ± 4.19 Control 26.89 ± 3.83	TAA 132.49 ± 27.19 Control 121.30 ± 15.00	TAA 81.86 ± 11.78 Control 77.71 ± 9.78
	Sampol [30]	2003	Spain	AD 19 (89.5) Control 19 (89.5)	AD 56.1 ± 11.9 Control 53.0 ± 9.5	AD 27.1 ± 3.1 Control 28.3 ± 2.8	NA	NA
	Zhang [33]	2014	China	AD 82 (85.4) Control 116 (74.1)	AD 50.17 ± 11.61 Control 53.82 ± 14.78	AD 25.73 ± 4.37 Control 24.62 ± 5.27	NA	NA
Retrospective cohort	Shih [31]	2018	China	OSA 31274 (75.27) Control 125096 (75.27)	OSA 44.82 ± 15.40 Control 45.03 ± 15.86	NA	NA	NA
Retrospective cohort	Teng [32]	2016	China	OSA 15848 (63.6) Control 39826 (63.8)	OSA 44.92 ± 17.34 Control 44.73 ± 17.46	NA	NA	NA
Prospective cohort	Zhang [33]	2014	China	OSA 64 (75.0) Control 52 (73.1)	OSA 54.72 ± 13.97 Control 52.71 ± 15.78	OSA 24.66 ± 5.74 Control 24.58 ± 4.69	NA	NA

OSA, obstructive sleep apnea; BMI, body mass index; BP, blood pressure; TAA, thoracic aortic aneurysm; AD, aortic dissection; NA, not available.

by echocardiography or cardiac MRI [24, 25, 26, 27, 28]. Three studies used echocardiography or computed tomography to identify AA and AD [29, 33], 2 studies used ICD codes [31, 32], and only 1 study did not refer to the diagnostic criteria [30]. Table 5 and Table 6 summarized the quality assessment of the included cross-sectional studies and cohort studies respectively. All cross-sectional studies were considered of moderate quality based on AHRQ. The NOS scores ranged from 5 to 9 reflecting a moderate to low risk of bias in cohort studies.

3.3. Outcome measures

3.3.1. Association between OSA and aortic diameter

Total 5 publications exploring the relationship between OSA and aortic diameter were identified for this analysis [24, 25, 26, 27, 28], with 2 studies conducted in patients grouped by different severity of OSA [27, 28]. The synthesized result showed that OSA was significantly correlated with increased aortic diameter (WMD = 1.46, 95% CI, 1.10–1.83, p <

Table 3. Outcomes of included studies investigating the association between OSA and aortic diameter dilatation.

Author	Number		Aortic diameter (mm)	OSA definition	Aortic measurement methods
	Non-OSA group	OSA group			
Chen [24]	14	65	OSA 31.6 ± 3.6 Control 29.2 ± 4.0	AHI≥15/h	conventional M-mode echocardiograph
Lee [25]	30	64	OSA 31.2 ± 3.4 Control 29.7 ± 3.0	OSA was defined as AHI ≥15 events per hour	transthoracic echocardiography
Hong [27]	78	Moderate-to-severe OSA n = 188 Mild OSA n = 86	Moderate-to-severe OSA 31.63 ± 3.74 Mild OSA 30.27 ± 3.79 Control 29.58 ± 3.61	OSA was diagnosed when apnea and hypopnea occurred more than 30 times in a 7-h sleep period or if the patients AHI was≥5	routine transthoracic echocardiography
Kwon [28]	87	Significant OSA n = 406 Mild OSA n = 215	Significant OSA 33.7 ± 3.6 Mild OSA 32.5 ± 3.4 Control 31.3 ± 3.5	AHI was≥5	routine transthoracic echocardiography
Sun [26]	50	136	OSA 28.51 ± 2.03 Control 27.62 ± 2.08	AHI≥5 per hour of sleep	conventional transthoracic echocardiography

OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; MRI, magnetic resonance imaging.

Table 4. Outcomes of included studies investigating the relationships between OSA and AA/AD.

Author	OSA prevalence		OSA definition	AA/AD diagnostic methods
	Control group	AA/AD group		
Gaisl [29]	49/104	131/208	OSA was defined as an apnea-hypopnea index≥5/h	aortic diameter exceeding the sex-specific cut-offs at the level of the sinus of Valsalva (≥39 mm for women, ≥44 mm for men) or the ascending aorta (≥42 mm for women, ≥46 mm for men)
Sampol [30]	13/19	13/19	Apnea-hypopnea index of more than 5	NA
Zhang [33]	78/116	67/82	OSA was diagnosed when the apnea-hypopnea index was ≥5 events/hr	Stanford's classification
	AA/AD incidence			
	Non-OSA group	OSA group		
Shih [31]	190/125096	36/31274	ICD-9-CM 780.51, 780.53, and 780.57	ICD-9-CM 441.1–441.9
Teng [32]	22/39826	11/15848	ICD-9-CM 780.51, 780.53, and 780.57	ICD-9-CM 441.0
Zhang [33]	0/52	2/64	OSA was diagnosed when the apnea-hypopnea index was ≥5 events/hr	Stanford's classification

OSA, obstructive sleep apnea; AA, aortic aneurysm; AD, aortic dissection; ICD, International Classification of Diseases; CM, Clinical Modification; NA, not available.

0.001) (Figure 2). Furthermore, patients with more serious OSA had a larger aortic diameter (WMD = 1.24, 95% CI, 0.75–1.73, p < 0.001) (Figure 3). There was no significantly statistical heterogeneity among these results.

3.3.2. Association between OSA and AA/AD

There are 3 cross-sectional studies [29, 30, 33] investigating the OSA prevalence in participants with or without AA/AD and 3 longitudinal

Table 6. Assessment of quality of included cohort studies (Newcastle-Ottawa Scale [NOS]).

Item	Study		
	Shih (2018)	Teng (2016)	Zhang (2014)
Selection	****	****	**
Comparability	**	**	*
Outcomes	***	**	**
Overall score	9	8	5

cohort studies [31, 32, 33] investigating the AA/AD incidence in participants with or without OSA. The meta-analysis of 3 cross-sectional studies [29, 30, 33] showed that the prevalence of OSA was significantly higher in patients with AA/AD compared to their counterparts without AA/AD (OR = 1.90, 95% CI, 1.30–2.76, p = 0.001). No evidence of heterogeneity was found (I^2 = 0.0%, P = 0.607) (Figure 4). However, the meta-analysis of 3 included cohort studies [31, 32, 33] showed that no significant difference in the incidence of AA/AD was found in individuals with or without OSA (RR = 0.85, 95% CI, 0.62–1.16, p = 0.307), with no significant heterogeneity observed (I^2 = 21.8%, P = 0.278) (Figure 5). Among 3 cohort studies, 2 studies [31, 32] used a Cox proportional-hazards regression model to determine the factors independently associated with AA/AD onset. For these two studies, the pooled HR was 1.16 (95% CI, 0.64–2.12, p = 0.626), further supporting that OSA was not associated with the occurrence of AA/AD after adjusting for age, sex, and comorbidity (Figure 5).

3.3.3. Sensitivity analysis

Due to the limited number of studies included in the meta-analysis, sensitivity analysis was only undertaken among studies investigating the association between OSA and aortic diameter. Omission of any individual study did not alter the overall result of pooled analysis, indicating that the result of meta-analysis was robust and persuasive (Figure 6).

4. Discussion

The present meta-analysis including 10 observational publications with 214,127 participants summarized available epidemiological evidences to evaluate the association between OSA and aortic diseases. Our results suggested that OSA was significantly associated with aortic
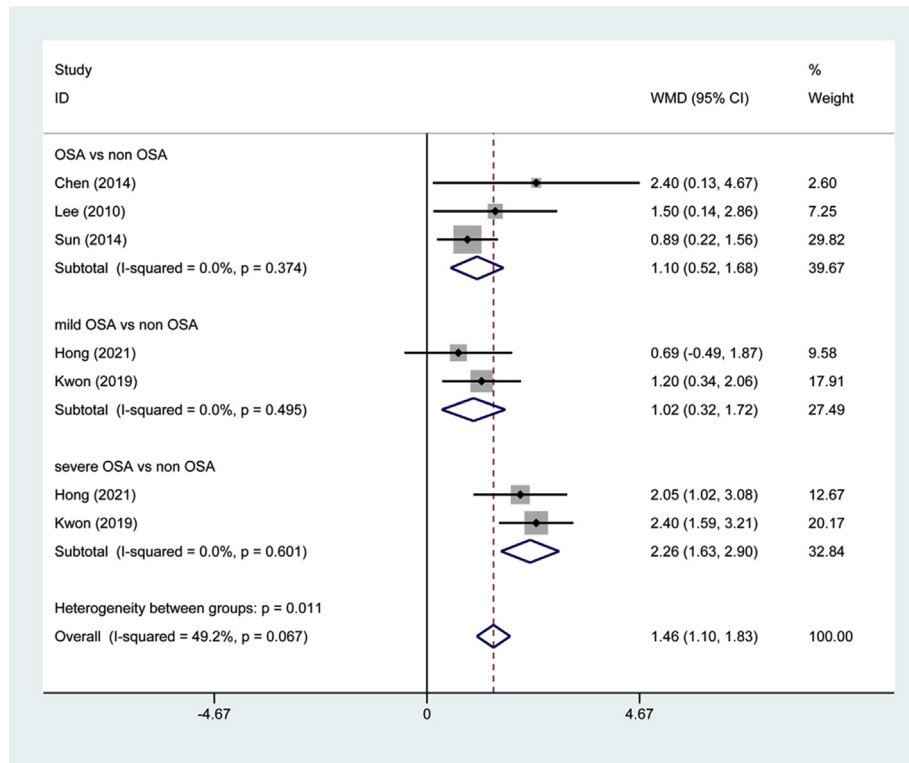
Table 5. Assessment of quality of included cross-sectional studies (Agency for Healthcare Research and Quality [AHRQ]).

Item	Study							
	Chen (2014)	Lee (2010)	Sun (2014)	Hong (2021)	Kwon (2019)	Gaisl (2020)	Sampol (2003)	Zhang (2014)
1) Define the source of information (survey, record review)	1	1	1	1	1	1	1	1
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	1	1	1	1	1	1	1	1
3) Indicate time period used for identifying patients	1	1	1	1	1	1	1	1
4) Indicate whether or not subjects were consecutive if not population-based	1	0	1	0	0	0	1	1
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	0	1	0	0	1	0	0	0
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	0	0	0	0	1	1	0	0
7) Explain any patient exclusions from analysis	1	0	0	1	1	1	1	1
8) Describe how confounding was assessed and/or controlled	1	1	0	1	1	1	0	1
9) If applicable, explain how missing data were handled in the analysis	0	0	0	0	0	0	0	0
10) Summarize patient response rates and completeness of data collection	0	0	0	0	0	0	0	0
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	0	0	0	0	0	0	0	0
Total	6	5	4	5	7	6	5	6

Figure 2. Forest plot of WMD of aortic diameter in patients with or without OSA.

diameter dilatation. However, OSA was not related to a greater risk of AA/AD occurrence.

The meta-analysis of 5 cross-sectional studies revealed an increase of aortic diameter in OSA patients and a positive correlation between OSA severity and aortic expansion. In line with this, Gherbesi *et al* conducted a meta-analysis using different inclusion criteria and found that aortic diameter was significantly larger in patients with OSA than that in non-OSA controls [34]. In addition to observational studies, recent experimental studies in humans supported the concept that OSA was associated with aortic expansion. Stöwhas *et al* reported that simulated obstructive hypopnea led to an increase in proximal aortic diameter in 20 healthy volunteers [16]. By using invasive examinations to quantitate transmural aortic pressure changes, Clarenbach *et al* further found that simulated OSA may mechanically contribute to aortic expansion by recurring transmural aortic pressure increase [35].

In contrast to aortic diameter dilatation, the meta-analysis of longitudinal cohort studies found no compelling evidence that OSA was related to an increased risk of advanced aortic events (AA and AD) although cross-sectional studies showed that the prevalence of OSA in AA/AD patients was higher than that in the control subjects. Further, we try to explain these two seemingly inconsistent results. First, compared to the cross-sectional study, the longitudinal cohort study affords more considerable statistical power to investigate a possible causal role of OSA in AA/AD development. Second, the meta-analysis of longitudinal studies included two nationwide population-based data [31, 32], which may be a more accurate reflection of aortic event incidence in OSA population. Third, the overlapping of the pathogenesis of OSA and AA/AD needs to be considered. For example, MMP9, a proteinase that degrade extracellular matrix [36], is responsible for aortic tissues degradation and AA formation [37], while the significant increase in the plasma levels of MMP9 may play an important role in the development of OSA [38]. Also,
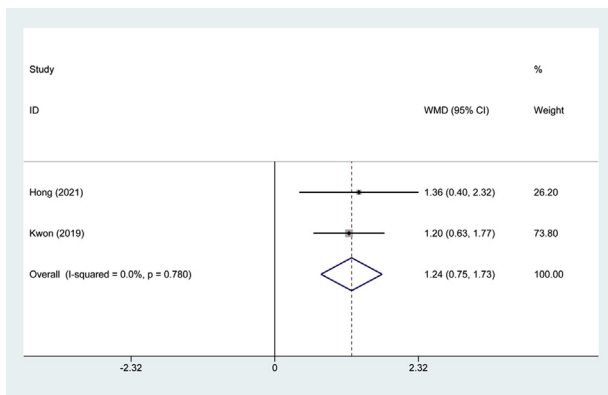

Figure 3. Forest plot of WMD of aortic diameter in patients with mild OSA or severe OSA.
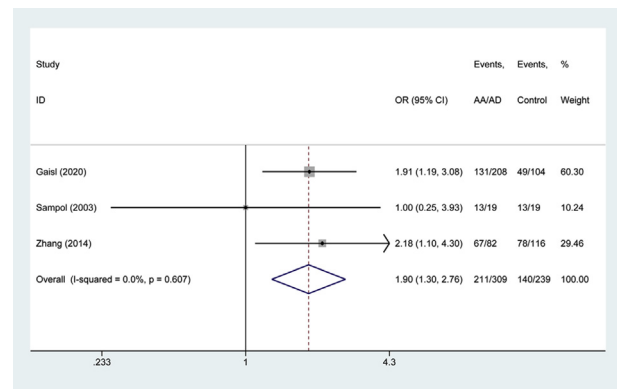

Figure 4. Forest plot of the prevalence of OSA in participants with or without AA/AD. AA, aortic aneurysm; AD, aortic dissection.
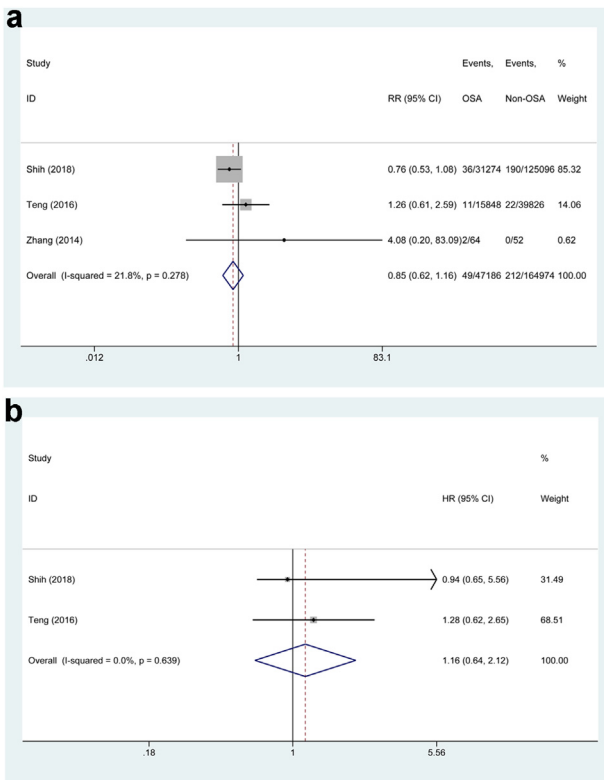
Figure 5. Forest plot of the incidence of AA/AD in participants with or without OSA.

older age, male gender and obesity are more likely to be suffering from AA/AD, while these risk factors could affect OSA [39]. These shared pathogenesis and risk factors make it difficult to determine the actual impact of OSA on aortic events. Lastly, contributory role of OSA to AA/AD is still controversial. Although OSA-induced intermittent hypoxia (IH), one of the main features of OSA, has been reported to act as a risk factor of AA and AD via the CaMKII-dependent MAPK [40] and ROS-H-IF-1α-MMPs-associated pathways [41], respectively, another study showed that IH inhibited inflammation and ECM degradation related genes, and alleviated thoracic AD in mice [42]. Therefore, these inconsistences require further investigation. Together, based on the above reasons, we speculate that although OSA was markedly associated with aortic diameter dilatation, this disease may not be enough to promote the occurrence of AA/AD due to the multifactorial pathogenesis of aortic diseases.

The present study is subject to several limitations of the included observational studies. First, the nature of the observational studies determines that we cannot draw precise conclusions regarding the causal relationship between OSA and aortic diseases. Second, age, sex and BMI existed potentially as important confounding factors in the meta-analysis of cross-sectional studies, which may interfere with our results. Third, the number and sample sizes of included studies were relatively small, which makes it difficult for us to separately evaluate the impacts of OSA on AA and AD. However, considering that AA and AD have many common risk factors (smoking, old age, male sex and family history, etc) and overlapped pathogenesis (hypertension and chronic inflammation, etc) and that OSA may influence the occurrence of AA and AD by some similar mechanisms, such as increased transmural pressure and arterial hypertension [20, 43], it may be feasible to explore the effects of OSA on AA and AD as a whole in this meta-analysis. Also, we did not distinguish between thoracic and abdominal aortic diseases because of the limited studies and data. Finally, all enrolled cohort studies were conducted in China, thus the results from these studies may not be generalizable to other ethnic populations. In the future, more longitudinal clinical studies including larger sample sizes and longer follow-up periods need to be conducted to help clarify the actual impact of OSA on the risk of aortic disease occurrence.

In conclusion, this meta-analysis summarized the current available epidemiological studies to explore the potential relationships between OSA and aortic disorder incidence. Our study proposed for the first time that OSA increases the risk of aortic diameter dilatation but does not affect AA and AD occurrence. Our results provide new information for understanding the role of OSA in the pathogenesis of aortic diseases.
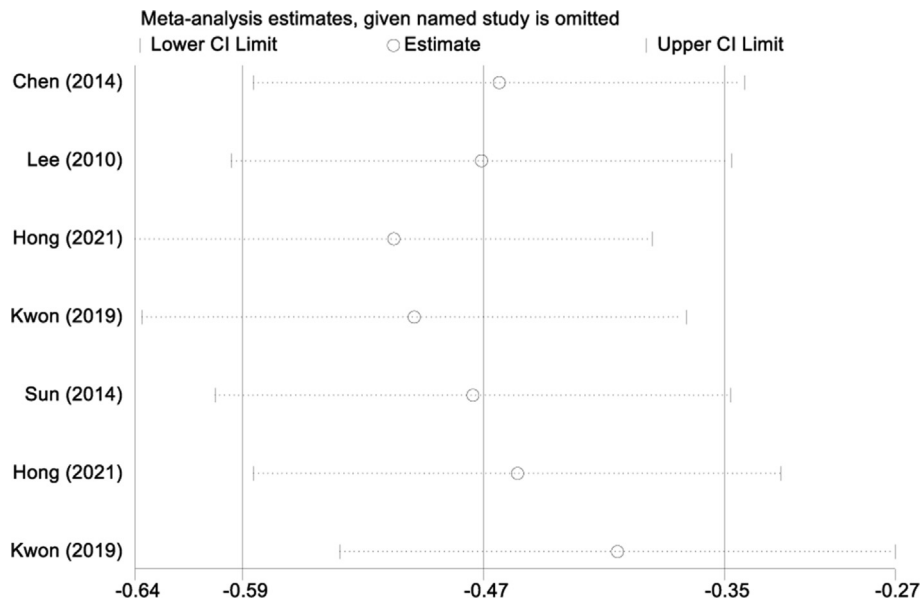

Figure 6. Sensitivity analysis for the effect of OSA on aortic diameter.

Declarations

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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