

# Association between obstructive sleep apnea (OSA) and atrial fibrillation (AF)

## A dose-response meta-analysis

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### Abstract

**Background:** Refractory hypoxemia episodes are characteristic of obstructive sleep apnea (OSA). Patients with OSA suffer from oxidative stress in all systems. Atrial fibrillation (AF) is a type of arrhythmia that may be induced by OSA. In this study, we explored the dose-response relationship between OSA and AF. Our research provides the basis for a novel approach to AF prevention.

**Methods:** We screened four databases (PubMed, Embase, the Cochrane Library, and Web of Science) for observational studies on OSA and AF. Studies were collected from database establishment to November 2020. We performed a traditional subgroup meta-analysis. Linear and spline dose-response models were applied to assess the association between the apnea-hypopnea index, an indicator of OSA severity, and the risk of AF. Review Manager version 5.3 software and Stata 16.0 were used for the analysis.

**Results:** Sixteen observational studies were included in the study. We excluded a study from the conventional meta-analysis. In the subgroup analysis, the odds ratios for new onset AF for no obvious reason, new onset AF after surgical operations, such as coronary artery bypass grafting, and AF after ablation treatment were 1.71 (95% CI 1.37–2.13,  $P < .05$ ), 2.65 (95% CI 2.32–3.01,  $P < .05$ ), and 2.93 (95% CI 2.47–3.49,  $P < .05$ ), respectively. Linear dose-response meta-analysis results revealed that the risk of AF increased with increasing apnea-hypopnea index value.

**Conclusion:** Through dose-response meta-analysis, we found a potential dose-response relationship between OSA severity and the risk of AF. This relationship should be considered in interventions aimed at AF prevention in the future.

**Abbreviations:** AF = atrial fibrillation, AHI = apnea-hypopnea index, CABG = coronary artery bypass grafting, NOS = Newcastle-Ottawa scale, ORs = odds ratios, OSA = obstructive sleep apnea, POAF = postoperative AF.

**Keywords:** AF, dose-response meta, meta, OSA

### 1. Introduction

Obstructive sleep apnea (OSA) is a common multifactorial disorder affecting both children and adults and is characterized by recurrent upper airway obstruction during sleep, leading to intermittent hypoxia.<sup>[1]</sup> All organs and systems are negatively affected by OSA, with cardiovascular consequences. However, OSA is an underdiagnosed condition with increasing prevalence, especially in men. According to Rojo-Sanchis et al<sup>[2]</sup> the prevalence of OSA is 5% to 25% in adults, 2% to 4% in males and 1% to 2% in females.

The apnea-hypopnea index (AHI) is an indicator of OSA severity and is used to determine whether to treat OSA.<sup>[3]</sup> The severity of OSA is classified into four categories based on the AHI: no OSA (AHI < 5), mild OSA ( $5 \leq \text{AHI} < 15$ ), moderate

OSA ( $15 \leq \text{AHI} < 30$ ) and severe OSA (AHI  $\geq 30$ ).<sup>[4]</sup> Moderate-severe OSA (AHI > 15) requires treatment with continuous positive airway pressure.<sup>[5]</sup> Intermittent hypoxemia activates the sympathetic nervous system, leading to myocardial remodeling and electrophysiological remodeling, suggesting a potential association between OSA and arrhythmia. The respiratory disturbance index, the total number of respiratory disturbances per hour, is another indicator used to evaluate OSA severity. In this research, we adopted the formula  $b = r \times \frac{s_y}{s_x}$  to estimate the AHI.

Atrial fibrillation (AF) is the most common arrhythmia observed in patients,<sup>[6]</sup> affecting 1% to 2% of the population worldwide,<sup>[7]</sup> and it is associated with increased cardiovascular mortality due to stroke and heart failure. AF has been proven to have an increasing prevalence with advancing

DZ and YM contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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age.<sup>[8]</sup> Qiu et al<sup>[9]</sup> reported that the morbidity of AF is 0.1% per year in patients aged 40 years and older. Previous studies found that AF and OSA were both present in high-risk groups.<sup>[10]</sup>

However, different types of AF have different characteristics. The fact that OSA was a risk factor for overall AF has been acknowledged. We wanted to determine the influence of OSA on different types of AF, which is more meaningful and applicable for clinical work. However, there seemed to be a lack of quantitative analyses on the relationship between OSA and AF. The AHI, as an indicator of OSA severity, is an independent variable that can be used for quantitative analysis. Here, we aimed to explore the relationship between the AHI and OSA. The results can be applied in the clinic and help physicians judge the risk of AF for OSA patients, which is advantageous for AF prevention. In the present research, 18 observational studies were included. We planned not only to explore the association between OSA and different subgroups of AF in a conventional meta-analysis but also to explore the dose-response relationship between AF and OSA severity in a dose-response meta-analysis. This study offers strong evidence and new thoughts on AF prevention.

## 2. Methods

We registered this systematic review and dose-response meta-analysis with the INPLASY registry (INPLASY2020120104). In addition, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for meta-analyses.

### 2.1. Study selection

In the present study, we included observational studies such as cohort studies, case-control studies and cross-sectional studies. The included studies all had clear outcomes and declared odds ratios (ORs), relative risks or hazard ratios and 95% confidence intervals for the association between OSA and AF. There were no restrictions on sex or age. We excluded studies in which indexes other than the AHI were used as indicators. Regarding the research type, case reports, fundamental studies and reviews were also excluded. The criteria for inclusion and exclusion are shown in Table 1.

### 2.2. Search strategy

We screened the PubMed, Embase, Cochrane Library and Web of Science databases. The retrieval time was from inception to November 2020. To meet the different demands of different databases, we modified the search terms and strategy. We screened all of the references of the included articles to ensure that we collected as many related studies as possible. Moreover, we communicated with senior specialists when possible to obtain additional references. The search strategy used in PubMed is shown in the supplementary materials, <http://links.lww.com/MD/H163>.

### 2.3. Study validation and data extraction

Two independent investigators (DZ, JX) extracted data from the included articles. Discrepancies were handled by consultation with and guidance from FY. Data regarding the baseline information of the participants, study design, and relevant statistics were extracted. No qualification was made to how AF severity was stratified.

We evaluated the included studies according to the Newcastle-Ottawa scale (NOS).<sup>[11]</sup> A quantitative scoring device proposed by the Cochrane Collaboration was adopted to assess the studies' methodological quality. The NOS assesses three areas: subject selection, comparability between groups, and outcome measures. The most extreme values for each area are four, two, and three, respectively. The lower the total score, the worse the methodological quality of the article is.

### 2.4. Data synthesis and analysis

Two investigators (DZ, YM) completed the conventional meta-analyses with Cochrane Review Manager software (version 5.3) to assess the risks of specific outcomes.

Heterogeneity among studies was evaluated with the use of  $I^2$  and  $P$ . We adopted a  $P$ -value of  $< .1$  to indicate statistical heterogeneity.<sup>[12]</sup>  $I^2$  describes the extent of variation due to heterogeneity rather than chance. The lower the  $I^2$ , the less variation is present.  $I^2 < 25%$  was considered to indicate little heterogeneity,  $25% < I^2 < 50%$ .  $I^2 > 50%$  indicated that there was enough heterogeneity to select a random-effects model. With  $I^2 < 50%$ , a fixed-effect model was employed.

For further analysis, we performed a dose-response meta-analysis using Stata version 16.0 software using a two-step method.<sup>[13]</sup> First, the correlation between the AHI and the risk of AF was evaluated with a spline model. In this spline model, we took the AHI as an independent variable and the OR/RR as a dependent variable. Second, we selected an appropriate merged model to merge the risk value for each study calculated in the first step due to heterogeneity.

### 2.5. Ethical approval

This study complied with the Declaration of Helsinki. Given that the study was a meta-analysis, no prior ethical approval was required. Informed consent was obtained from all subjects involved in each included study. In addition, written informed consent was obtained from the patients to publish the papers included in this meta-analysis.

## 3. Results

### 3.1. Selection of studies

The initial search identified 1940 articles according to the inclusion criteria and exclusion criteria. After reviewing the titles and abstracts, 42 articles remained, with ten extra articles identified from reference lists. Then, we screened whole texts, and 16 articles were selected. The studies were from America, Europe and Asia and had a variety of design types, including cross-sectional, cohort and case-control.

**Table 1**

#### The criteria for inclusion and exclusion.

Criteria for inclusion	Criteria for exclusion
Patients with OSA or AF	All kinds of reviews, case reports, or fundamental researches
Researches provide accurate risk ratio or odds ratio and 95% confidence intervals	No clear outcome or selected other cardiovascular diseases as cases outcomes
All kinds of cross-section studies, cohort studies, or case-control studies	Without a control group
	No integrated hazard ratio risk ratio or odds ratio

AF = atrial fibrillation, OSA = obstructive sleep apnea.

**Table 2**  
The baseline characters of the included studies.

Study	Country	Participant	AF sample size	Prevalence of AF (%)	Study design	Female	Age range/mean age (yrs)
Uchôa 2015	Brazil	67	10	14.92537313	Prospective study	25%	58 ± 8
feng2019	US	506,604	183,075	36.13769335	Retrospective cohort study	31.80%	66.2 ± 12.1
gali2020	US	8612	2502	29.0524849	Retrospective cohort study	34.50%	62.9 ± 13.8
wong2015	US	545	226	41.46788991	Retrospective cohort study	13.21%	66.15
zhao2015	Singapore	160	35	21.875	Prospective study	NR	62.8
chilukuri2009	US	210	45	21.42857143	Prospective study	20%	58 ± 10
chilukuri2010	US	109	34	31.19266055	Prospective study	21%	60 ± 10
jongnarangsin2008	US	324	127	39.19753086	Prospective study	24%	57 ± 11
neilan2013	US	720	720	100	Retrospective cohort study	NR	NR
gami2007	US	3542	133	3.754940711	Retrospective cohort study	44%	49 ± 14
mehra2006	US	566	566	100	Retrospective cohort study	NR	69.4
Mehra 2009	US	2911	138	4.740638956	Cohort study	NR	76.4 ± 5.4
Selim 2016	US	697	38	5.451936872	Cross-sectional analysis	5.46%	58.69
Kendzerska 2018	Canada	8256	173	2.095445736	Prospective study	28%	47
Cadby 2015	Australia	6841	455	6.651074404	Prospective study	23%	48.3 ± 12.5
anzai2020	US	709	39	5.500705219	Cross-sectional study	0	83.2 ± 3.1

AF = atrial fibrillation, NR = not reported.

**3.2. Characteristics and quality of the included studies**

There were a total of 16 observational studies included in this research. Participants were involved. The included studies were different sizes (67 to 506,604), with different proportions of females (0–44%). A total of 3361 new cases of AF were diagnosed. The prevalence of AF in patients with OSA was approximately 34.61%. The baseline characteristics of each included study are listed in Table 2. The NOS score for each included study is shown in Table 3. The NOS evaluated the articles in three dimensions (selection quality, comparability and outcome/exposure quality) according to the corresponding criteria. Every asterisk represents one point, and we calculated the total number of points as the NOS outcome for each study. The NOS score remained high (mean score = 6.66), and every study scored more than 5 on the NOS, which means that the studies we selected had high enough quality for meta-analysis.

**3.3. Meta-analysis results**

The included studies were divided into two groups, one for conventional meta-analysis and the other for dose-response

meta-analysis. The studies included in the dose-response group all researched the correlation between AHI levels and the risk of AF occurrence. For the conventional group, the researchers only studied the association between OSA and AF. In the conventional meta-analysis, the result for overall AF was OR = 2.54 (95% CI 2.20–2.92, *P* < .05) (Fig. 1A). However, *I*<sup>2</sup> = 68% (*P* = .004) (Fig. 1B) indicated heterogeneity in the analysis. To further explore the source of heterogeneity, the funnel plot indicated that the results from Cadby et al<sup>[14]</sup> and Wong et al<sup>[15]</sup> were outside of the 95% CI for overall AF. These were the main sources of heterogeneity.

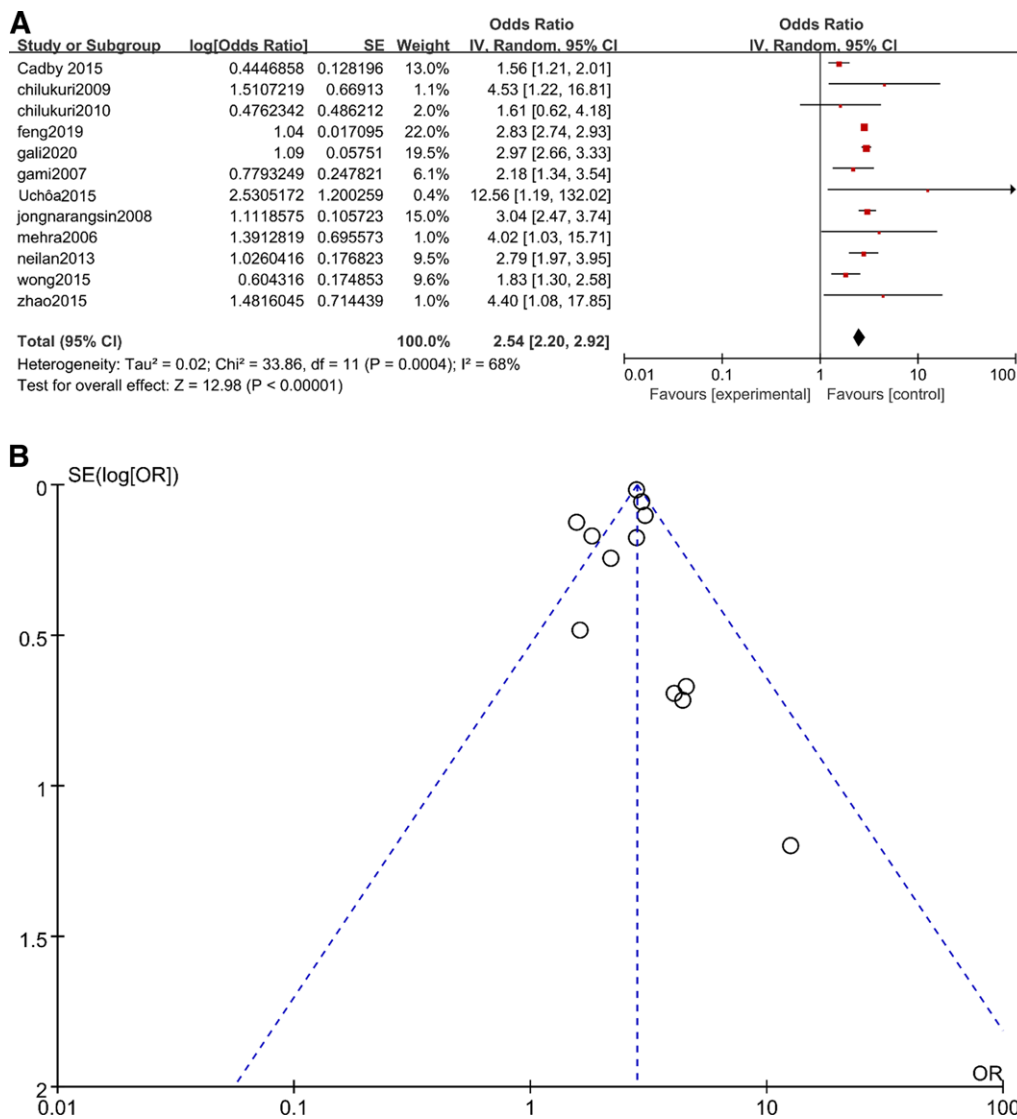
The heterogeneity in the overall AF results showed that there existed a difference between each study and the others. Therefore, we performed a subgroup analysis on AF type. Briefly, the included studies were divided into three subgroups: new onset with no obvious reason, new onset after surgical operations, such as coronary artery bypass grafting (CABG), and AF after ablation treatment.

The results of the three subgroups were OR = 1.71 (95% CI 1.37–2.13, *P* < .05) (Fig. 2A), OR = 2.65 (95% CI 2.32–3.01, *P* < .05) (Fig. 3A) and OR = 2.93 (95% CI 2.47–3.49, *P* < .05), respectively (Fig. 4A). The heterogeneity results for these three subgroups were as follows: 33% (*P* = .23) (Fig. 2A),

**Table 3**  
The NOS scale of the included studies.

Study	Selection	Comparability	Exposure	Total
anzai2020	**	**	**	6
cadby2015	***	**	**	7
feng2019	**	**	***	7
gali2020	**	**	**	6
gami2007	**	*	***	6
mehra2006	**	**	***	7
neilan2013	**	**	**	6
wong2015	**	**	***	7
zhao2015	**	**	***	7
Uchôa 2015	***	**	**	7
chilukuri2009	**	**	***	7
chilukuri2010	**	**	***	7
jongnarangsin2008	**	**	***	7
kendzerska2018	**	**	***	7
selim2016	**	**	**	6
Mehra2009	**	*	***	6

NOS = Newcastle-Ottawa scale.



**Figure 1.** (A) Meta-analysis of OSA and risk of AF using random-effects models. (B) Funnel plots for assessment of publication bias among all included studies in the overall AF meta-analysis. AF = atrial fibrillation, OSA = obstructive sleep apnea.

57% ( $P = .05$ ) (Fig. 3A) and 0 ( $P = .54$ ) (Fig. 4A), respectively. We could judge from the funnel plots that there were no studies outside of the 95% CI for any subgroup (Fig. 2B, Fig. 3B and Fig. 4B). The results above revealed that subgroup analysis could significantly reduce the heterogeneity. The heterogeneity in the overall analysis was mainly due to the variety of AF types included in the overall analysis.

### 3.4. Dose-response meta-analysis

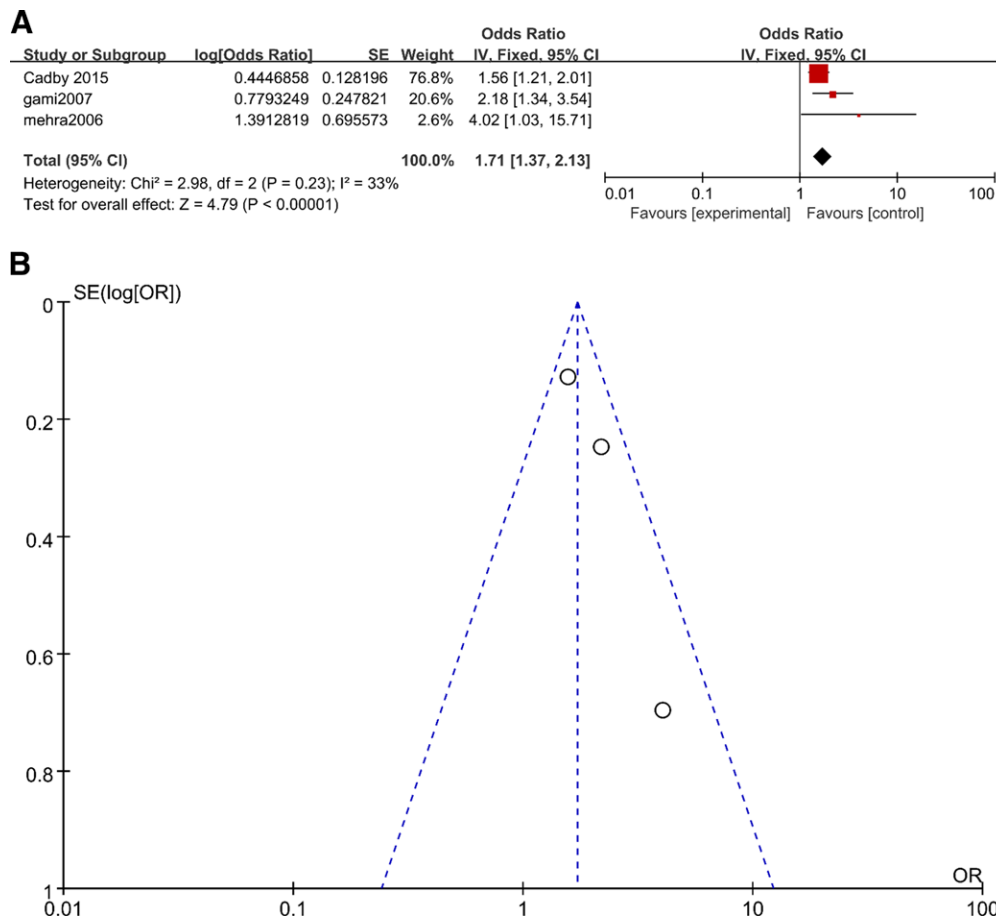
We performed a dose-response meta-analysis for new onset AF and different OSA severities to further explore the relationship between OSA and AF. We constructed linear and spline models. The spline analysis showed no association between the AHI and AF ( $P > .05$ ). Therefore, we performed a restricted spline analysis to model the linear dose-response association, and the model indicated an increased risk of AF with increased OSA severity. The linear analysis revealed that the risk of AF occurrence increased by 1.26% (95% CI 0.86%–1.67%,  $P < .05$ ) for each event per hour increase in AHI (OR = 1.013 95% CI 1.009–1.017,  $P < .05$ ) (Fig. 5).

## 4. Discussion

In the present study, we performed a traditional meta-analysis and a dose-response meta-analysis to explore the correlation between OSA and the risk of AF in depth. Not all of the included primary studies concluded that OSA is a risk factor for the occurrence of AF. Moreover, the associations between different OSA severities and different AF types were not the same.

The conventional meta-analysis revealed that OSA was associated with the overall risk of AF ( $P < .05$ ). However, heterogeneity reduced the reliability. Therefore, we performed a subgroup analysis. The results of the subgroup analysis revealed that OSA was associated with different AF types, including new-onset AF, AF after surgery and recurrent AF.

Moore et al<sup>[16]</sup> observed that patients with OSA had a higher risk for postoperative AF (POAF) after CABG. However, they did not draw a clear conclusion regarding whether other variables played key roles in the development of POAF. In our research, after normalization of the original data, we were able to examine the influence of OSA on AF. The results indicated that OSA could be an independent risk factor for POAF.



**Figure 2.** (A) Meta-analysis of OSA and risk of new-onset AF using fixed-effects models. (B) Funnel plots for assessment of publication bias among all included studies in the new-onset AF subgroup meta-analysis. AF = atrial fibrillation, OSA = obstructive sleep apnea.

In previous studies,<sup>[17,18]</sup> researchers proved that patients with OSA had a higher likelihood of AF recurrence and that continuous positive airway pressure benefited those patients. However, these studies defined AF recurrence as AF reappearing after successful treatment by antiarrhythmic drugs, electrical cardioversion, and catheter ablation. This limit the extension of their conclusions. In the present research, we focused on AF recurrence after ablation treatment. The results revealed that OSA significantly increased the risk of AF recurrence in patients who underwent AF ablation therapy.

Different researchers have reported different ORs for the association of OSA and new-onset AF, and in some cases, the discrepancies are significant. Due to data normalization, our results seem to be conservative. To perform a more precise analysis, we decided to explore the relationship between OSA severity and AF. In the dose-response meta-analysis, the results indicated a positive correlation between the AHI and the OR of new-onset AF.

**4.1. Analysis of heterogeneity**

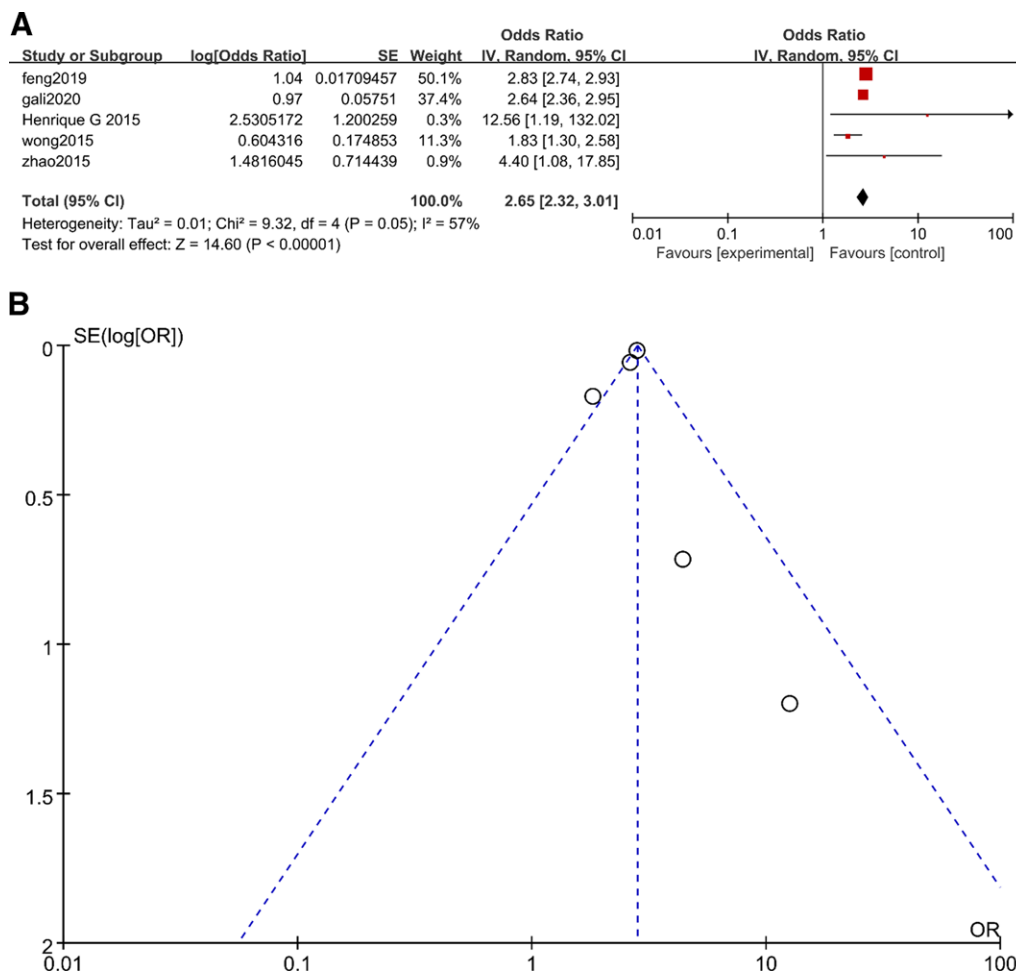
In the meta-analysis of different AF groups, heterogeneity was present at a moderate level when merging the overall AF data from similar studies. In further subgroup analysis, the heterogeneity was effectively reduced. This revealed that the heterogeneity was mainly due to the different AF subtypes. The association between OSA and overall AF was reasonable but should be considered with caution. In the funnel plots, we verified that the primary sources of heterogeneity

were Cadby et al<sup>[14]</sup> and Jongnarangsin et al<sup>[19]</sup> We speculated that the heterogeneity might be due to the following reasons. First, there were different proportions of age and sex among the participants in the included studies. According to Senaratna et al,<sup>[20]</sup> OSA prevalence and severity are higher in males and at older ages. We found that most of the included studies included more male than female patients. Briefly, the larger the male constituent ratio and the older the mean age, the higher the prevalence of AF will be. Furthermore, studies containing more women show a lower OR for AF. Sex-based differences introduced great heterogeneity to our research. Second, we did not match other factors. Some studies normalized their results, but others did not. For example, Chilukuri et al<sup>[21]</sup> used multivariate analysis, and Gami et al<sup>[22]</sup> selected univariate analysis. The multivariate analysis eliminated the errors from other factors, which led to a conservative result. This would surely introduce heterogeneity into the meta-analysis. Finally, the included studies had different study designs. Four were case-control studies, while the remaining six were cohort studies.

**5. Dose-response meta-analysis**

**5.1. Comparison with similar studies**

There have been no dose-response meta-analyses on the association between OSA and AF to date. Our research provided strong evidence that OSA is related to the risk of new-onset AF occurrence, and we analyzed the OR for AHI dose with linear and spline models. The results were consistent with



**Figure 3.** (A) Meta-analysis of OSA and risk of AF after surgery using random-effects models. (B) Funnel plots for assessment of publication bias among all included studies in the AF after surgery subgroup meta-analysis. AF = atrial fibrillation, OSA = obstructive sleep apnea.

previous traditional meta-analyses and other studies. Both models revealed that OSA was closely related to new-onset AF, especially at high AHI doses.

### 5.2. Possible mechanisms

OSA is characterized by intractable hypoxemia,<sup>[23]</sup> which leads to various pathologic conditions, including neural activation, systemic inflammation, oxidative stress loading, and hormone disorder.<sup>[24–27]</sup> There are many potential reasons for OSA leading to AF. Hypoxemia, pressure surges, and sympathetic activation are all potential mechanisms.<sup>[28]</sup> In addition, it has been proven that OSA increases the level of C-reactive protein, which is an independent predictive factor for the development of AF.<sup>[29,30]</sup> Moreover, intractable hypoxemia may cause mechanical and electrical changes in OSA patients.<sup>[31]</sup> These changes may lead to conditions conducive to AF. Another critical role in this process is an autonomic mechanism. Basic research studies have proven that cardiac autonomic ganglia ablation suppresses AF in a canine model of acute intermittent hypoxia.<sup>[32]</sup>

Our research has proven that OSA is a risk factor for AF. In addition, for different AF types, there are different ORs for OSA. OSA is a significant risk factor for patients who have undergone surgical operations such as CABG. Moreover, OSA is an essential factor in AF recurrence, which indicates that doctors should pay more attention to patients' breathing during sleep after ablation treatment. For new-onset AF, the severity of OSA is

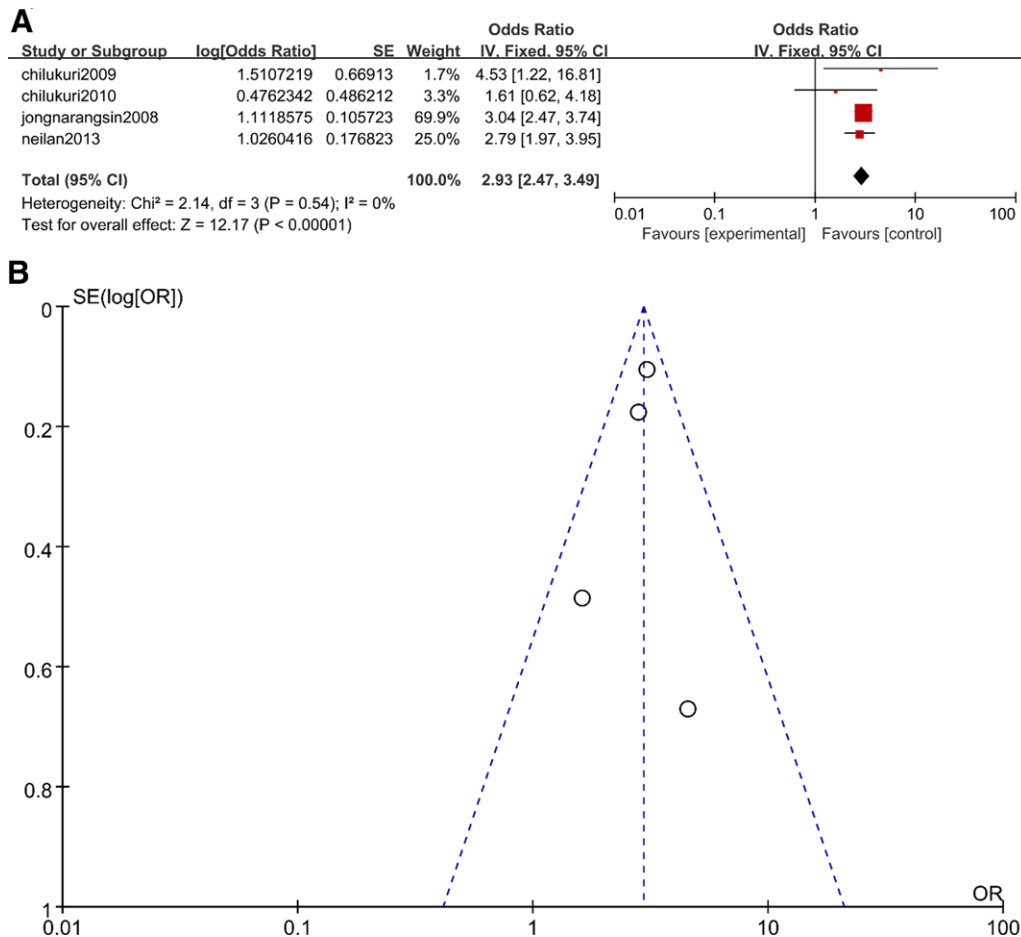
positively related to the OR of AF. In this study, we constructed a dose-response model for AHI and new-onset AF. With the help of the model we built, physicians will have more evidence for clinical decision making regarding intervention timing for OSA patients to prevent AF.

### 6. Limitations

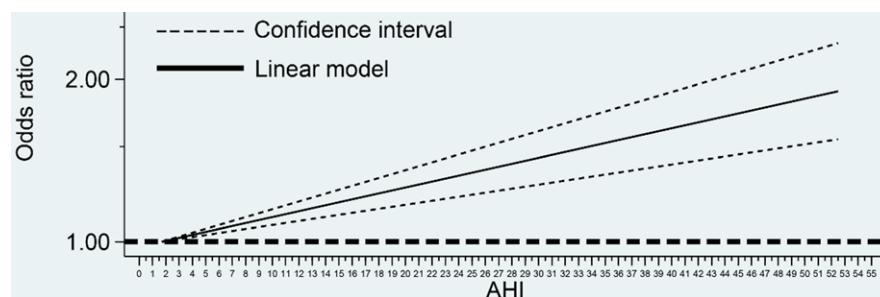
There are a few limitations to our research. First, some studies' sample sizes were limited. Uchôa et al<sup>[33]</sup> only included 67 samples. Fewer subjects might yield a lower confidence level. This could be a reason for the heterogeneity. Second, when constructing the linear and spline models, we needed as much data as possible. The limited number of included studies introduced errors to the regression. Third, the measurement of OSA was inconsistent. The different measurement techniques might influence the AHI. In future studies, there may be challenges in selecting the timing of treatments for OSA. It will be necessary for doctors to choose appropriate opportunities to best benefit patients.

### 7. Conclusion

In summary, our study concluded that OSA was correlated with the risk of AF occurrence regardless of AF subtype. In the subsequent dose-response meta-analysis, we concluded that the AHI was positively related to new-onset AF. Further studies are needed to assess treatment timing for OSA patients according to their AHI for AF prevention.



**Figure 4.** (A) Meta-analysis of OSA and risk of recurrence AF using fixed-effects models. (B) Funnel plots for assessment of publication bias among all included studies in the recurrence AF subgroup meta-analysis. AF = atrial fibrillation, OSA = obstructive sleep apnea.



**Figure 5.** Linear dose-response relationship between AHI and the risk of AF. The dashed line represents 95% CI. AF = atrial fibrillation, AHI = apnea-hypopnea index.

**Author contributions**

Software: Dong Zhang.  
 Writing – original draft: Dong Zhang.

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