Obstructive Sleep Apnea Syndrome Associated with Atrial Fibrillation in Adult Patients: A Systematic Review and Meta-Analysis

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Abstract: *Introduction*: Obstructive sleep apnea syndrome (OSAHS) is a common disease. However, its diagnosis and treatment are underestimated. The main reason is that the upper airway completely or partially collapses, leading to repeated sleep apnea episodes. In addition, atrial fibrillation(AF) is the most frequent arrhythmia in the world, these two entities may be related and are important public health problems.

Objective: To determine the association between obstructive sleep apnea syndrome and atrial fibrillation in adult patients.

Materials and Methods: A systematic review and meta-analysis of observational studies that associate obstructive sleep apnea syndrome and atrial fibrillation was carried out. The search was carried out in 4 databases: PUBMED, Web of Science, Embase, Scopus.

Results: Eight studies were included (n=562241). A significant association was found between obstructive sleep apnea and atrial fibrillation (OR: 1.38; 95% CI 1.24 to 1.54). In addition, low heterogeneity was found between studies I2: 13%.

Conclusions: It was found that obstructive sleep apnea and atrial fibrillation are significantly associated.

Keywords: Sleep Apnea, Obstructive, Obstructive Sleep Apnea, Atrial Fibrillation, Systematic review, Sleep syndrome, public health (Source: MeSH NLM).

INTRODUCTION

Obstructive sleep apnea syndrome (OSAHS) is characterized by recurrent episodes of partial or total occlusion of the upper airway during sleep [1]. In 2019, it was estimated that OSAHS affected around one billion people, with a prevalence higher than 50% in some countries [2].

Globally, the number of people affected by obstructive sleep apnea was highest in China, with a total of 176 million people with OSAHS, followed by the US, India, and Brazil [2]. The population of Latin America and Asia has a higher incidence than European countries, especially in Brazil, Colombia, Chile, and Mexico [3].

Although OSAHS has classically been limited to the respiratory system, evidence demonstrates the association between OSAHS and the cardiovascular system [1]. Some studies have found a significant relationship between this and atrial fibrillation; However, their relationship is not so clear yet [4]. But there has not yet been a complete analysis evaluating if this association exists and its magnitude. For this reason, in the present investigation, a systematic review and meta-analysis were carried out to determine the association between OSAHS and AF.

METHODS

Design

A systematic review (SR) with meta-analysis of observational studies. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses was used to guide this study [5].

Search Strategy

This work was carried out using search strategies in four databases: Pubmed/Medline, SCOPUS, Web of Science, and EMBASE. The main information search strategy included the following keywords: Sleep Apnea Syndromes and Atrial Fibrillation. Within-domain search terms were combined with 'OR' and cross-domain terms with 'AND'. No temporal delimitation of

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the studies or language filter was applied, but exceptions were made if they did not meet the selection criteria.

Selection Criteria

The inclusion criteria were: 1) studies that aimed to evaluate OSAHS and AF in patients older than 18 years; 2) analytical studies that presented a comparison group; and 3) in English, Portuguese or Spanish. While the following were excluded: 1) studies not available in their complete version; 2) case reports, letters to the author, narrative reviews, or systematic reviews; and 3) if they have associated heart disease; 4) articles that did not provide the values of the odds ratio (OR) or relative risk (RR) and the 95% confidence interval.

Studies Selection

The Rayyan online software (https://rayyan.qcri.org) was used, and three researchers (BMGC, OGC, and GG) independently reviewed the titles and abstracts of all the citations found, thus classifying the citations as " included", "excluded" or "doubtful". Subsequently, the results of each investigator were compared. In case of discrepancy, the participation of a fourth investigator (VJVP) was requested to make the final decision.

After that, the full-text review of all the citations that have been included was carried out. For this, the same methodology mentioned above was used, performing a triple check. In an Excel sheet, it was placed whether the study should be included or not. If it was not included, the reasons were placed. This procedure was also carried out by three researchers (BMGC, OGC and GG).

Data Extraction and Qualitative Analysis

The articles that remained stopped for data extraction were placed in a file prepared in Microsoft Excel 2016. The following information was extracted from each selected article: first author, year, country, study design, follow-up time, sample size, sex (% Male), mean with standard deviation (SD) or median with the interquartile range (IQR) of age, study population (selection criteria), cut-off point to define OSAHS, the measure of association used, the adjustment variables.

Risk of Bias Assessment

The Newcastle-Ottawa Scale (NOS) was utilized to assess the level of bias of the studies [6]. The NOS evaluates each manuscript based on selection, comparability, and outcome. A total of 9 points can be obtained. The NOS classification as follows: ≥7 indicates low risk, while <7 indicates high risk. The three researchers mentioned above did the evaluation independently and then compared their results. If there were discrepancies, this was resolved by the fourth investigator.

Quantitative Analysis

A random effects meta-analysis was performed in the Review Manager 5.4 program for the statistical analysis to measure the relationship between both variables of interest. The association measure used was the odds ratio (OR), with its respective 95% confidence interval (95% CI).

Heterogeneity was identified by the I squared (I^2) [7]. This was interpreted according to the Cochrane manual: 0 to 40% = might not be important; 30 to 60% = may represent moderate heterogeneity; 50 to 90% = may represent substantial heterogeneity; 75 to 100% = considerable heterogeneity [8]. Due to heterogeneity, a randomized model analysis was performed.

Ethical Aspects

This study is a secondary analysis of primary studies published in scientific journals, so the risks to people who were part of the studies are minimal. In addition, this was approved by the Research Ethics Committee of the Facultad de Medicina Humana de la Universidad Ricardo Palma.

RESULTS

Eligible Studies

Two thousand seven hundred eighty-six publications were identified. After removing 652 duplicates, 2134 manuscripts were evaluated by title and abstract. After excluding 2076 studies, a total of 58 full-text articles were obtained. Finally, after applying the selection criteria, he was left with 8 articles (Figure **1**).

Study Characteristics

Table **1** shows the main characteristics of the studies included (n= 562 241). Samples ranged from 555 to 506,604 participants in each study. The male sex was the most prevalent in the studies with percentages from 44% to 79.6%. Meanwhile, the average age in the studies is around 45 and 62 years.

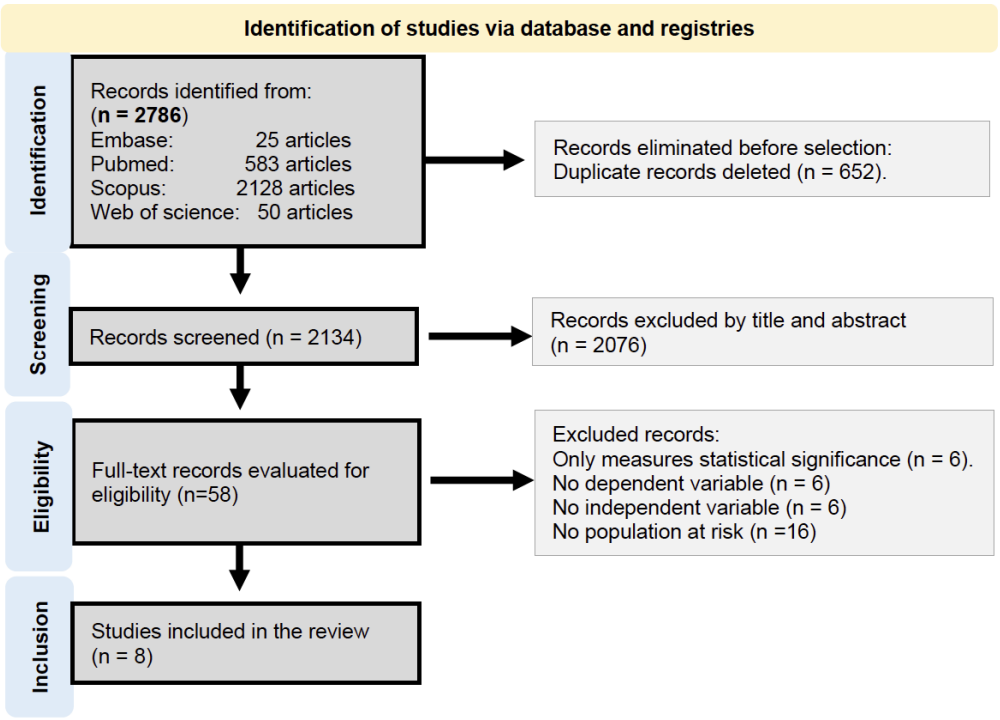

Figure 1: PRISMA 2020 flowchart for systematic reviews.

Risk of Bias Assessment

The eight selected studies were assessed using the New Castle Ottawa risk of bias tool. Selection scores were homogeneous across studies. In the score and general judgment, it was of low level of bias and an article with a moderate risk of bias. Publication bias due to the small number of articles was not assessed (Table **2**).

Meta-Analysis of Apnea and Atrial Fibrillation

The studies by de Apoor S Gami *et al*. (OR: 2.18; CI: 1.34-3.54) presented a statistically significant association [9], Yu-Sheng Lin *et al.* (OR: 1.63; IC: 0.78-3.40) [10], Haobo Xu *et al*. (OR: 1.58; IC: 0.84 - 2.97) [11], by Nicola J. Adderley *et al.* (OR: 1.53; IC: 1.28-1.83) [12], from Samir V. Patel, MD *et al*. (OR: 1,4; IC: 0,6-3,6) [13], Neel J Patel, M.D. *et al.* (OR: 1.3; IC: 1.0-2.4) [14], by Lama Ghazi *et al.* (OR: 1.27; IC: 1.13-1.44) [15], and by T Robert Feng *et al.* (OR: 1.04; IC: 1.01–1.08) [16].

DISCUSSION

Atrial fibrillation is the most common cardiac arrhythmia, affecting approximately 33 million people worldwide. This is why it is considered a significant public health problem, given its high morbidity and mortality and economic burden associated with thromboembolic complications [4]. Numerous studies indicate the association of sleep apnea as a cause of atrial fibrillation, establishing a complex pathophysiological framework that determines that both entities are frequently concomitant in many patients [17].

In the present study, there is an average age between 45 and 66 years in the population; taking into account that the prevalence of atrial fibrillation increases with age, ranging from 0.1% among persons under 55 years of age and 3.8% to 4.2% among persons 60 years of age or older; the sample of the population would not be characteristic because the prevalence of atrial fibrillation could be from 9 to 17% in those over 80 years of age. However, the cardiovascular risk associated with obstructive sleep apnea may decrease with age, being more predominant in adults under 60 years of age according to the Sleep Heart Health Study [18-20].

A higher proportion of affected men has been obtained in the study, being between 56% and 79% of the populations; accordingly, The reports from the Framingham Heart Study and the Olmstead County Study report higher incidence figures for men (3.8-4.7 cases per 1000 person-years) compared to women (1.6-2.7 cases per 1000 person-years) with atrial fibrillation and the overall prevalence of obstructive sleep apnea of 13.8% in men and 6.4% in women [21-23].

Table 1: Main Characteristics of the Studies Included

First Author	Year	Country	Study design	Follow-up time	Sample size	Sex (%Male)	Mean (SD) or median (IQR) age	Study population (selection criteria)	Cut-off point	Measure of association	Results	Adjustment variables
Yu-Sheng	2017	Taiwan	Retrospective Cohort	2000-2010	16189	79.40%	43.9 12.2 (OSAHS)	18 years of age or older,	ICD 9	OR: 1.63 ; CI: 0.78-3.40; P=0.193	Atrial fibrillation	Age, sex and Charlson comorbidity index.
							43.8 12.1 (NO OSAHS)	recently diagnosed with OSAHS				
Patel	2017	United States of America	Cohort	—	674	56%	63 ± 13	Adults, undergoing overnight polysomnography and at least one 12-lead electrocardiogram, DNA samples	AHI ≥5	OR: 1.3 ; CI: 1.0- 2.4	Atrial fibrillation	Age, sex, body mass index, ancestry, hypertension status, and heart failure status.
8United8	United States of America	Prospective cohort	2003–2007	20.351	44.87%	62.5 ± 8.5 (HR OSAHS)	Older than 45 years old, Berlin questionnaire completed	High risk of OSA (Berlin Sleep Questionnaire)	OR: 1.27 ; CI: 1.13-1.44	Atrial fibrillation	Pulse pressure, age, sex, race, region and socioeconomic status, previous medical conditions, physiological markers and health behaviors.	
						64.9 ± 9.2 (LR OSAHS)						
Samir	2018	United States of America	Prospective cohort	2013-2015	209	73.20%		18 years of age or older, undergoing CABG	ICD 9	OR: 1,4 ; CI: 0,6-3,6; p=0,50	Atrial fibrillation	Age, sex, race, OSAHS status, obesity, hypertension, DKA, thyroid disorders, CKD, diabetes, COPD, and CHF.
Feng	2019	United States of America	Retrospective cohort	2007–2014	506.604	68.20%	66.2 ± 12.1	Over 18 years of age, undergoing CABG and/or valve surgery.	ICD 9	OR: 1.04 ; CI: 1.01-1.08; p < 0.01	Atrial fibrillation	-

(Table 1). Continued.

First Author	Year	Country	Study design	Follow-up time	Sample size	Sex (%Male)	Mean (SD) or median (IQR) age	Study population (selection criteria)	Cut-off point	Measure of association	Results	Adjustment variables
Xu	2020	China	Retrospective cohort	2010 - 2018	555	71.17%	45.4 ± 13.7 (no OSA)	Diagnosed with HCM, undergoing a first overnight sleep diagnostic test	AHI: > 5	OR: 1.58 ; CI: 0.84-2.97 ; p= 0.153	Atrial fibrillation	Age, sex, BMI, New York Heart Association class, left atrial diameter, hypertension, oxygen desaturation index and obstructive hypertrophic cardiomyopathy. (HCM)
							53.7 ± 11.2 (OSA)					
Adderley	2020	United Kingdom	Retrospective cohort	2005 - 2018	14117	75.03%	60.07 ± 10.56 (OSA)	16 years and older, type II diabetes	Presence of OSA	OR: 1.53 ; CI: 1.28- 1.83	Atrial fibrillation	Age, sex, BMI, smoking, Townsend quintile, lipid-lowering drug prescription, antiplatelet drug prescription, antihypertensive drug prescription, insulin prescription, ethnicity, duration of diabetes, HbA1c category, and CCI
							60.99 ± 9.08 (no OSA)					
Gami	2007	United States of America	Retrospective cohort	4.7 years	3,542	66%	49 (14)	Adults, first polysomnography performed with OSA without the presence of AF at the time.	AHI ≥5	OR: 2.18 ; CI: 1.34-3.54	Atrial fibrillation	-

Table 2: Risk Assessment of the Studies Included in the Review

First author	Year	Selection				Comparability		Result			Score	Overall Judgement
		Representativeness of exposed cohort	Selection of unexposed cohort	Determination of exposure	Outcome not present at baseline	Study controls for sex and age	Study controls for any additional important factors	Outcome assessment	Duration of follow-up	Adequacy of follow-up		
Yu-Sheng	2017	*	*	*	*	*	*	*	*	*	9	Low Risk
Patel	2017	-	-	*	*	*	*	*	-	-	5	Moderate Risk
Lama	2018	*	*	*	*	*	*	*	*	*	9	Low Risk
Patel	2018	*	*	*	*	*	*	*	*	*	9	Low Risk
Feng	2019	*	*	*	*	-	-	*	*	*	7	Low Risk
Xu	2020	-	-	*	*	*	*	*	*	*	7	Low Risk
Adderley	2020	*	*	*	*	*	*	*	*	*	9	Low Risk
Gami	2007	*	*	*	*	-	-	*	*	*	7	Low Risk

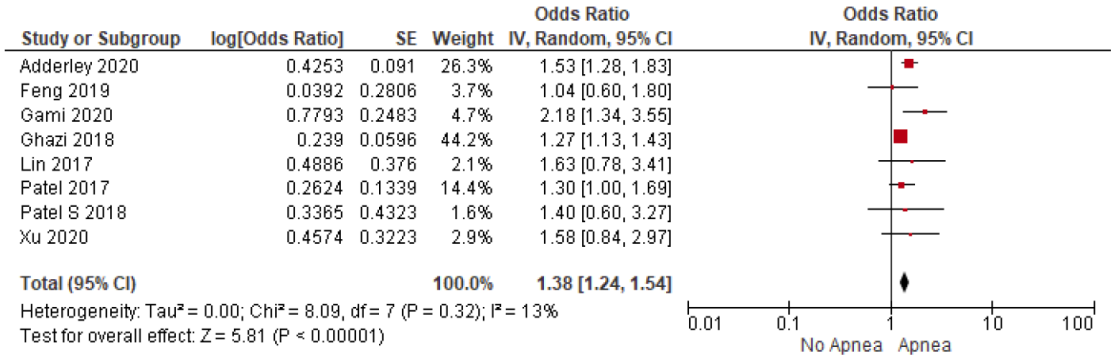

Figure 2: Forest plot of the association of obstructive sleep apnea and atrial fibrillation in adult patients.

Among the studies there are different ways to select patients with obstructive sleep apnea (OSA) using the ICD 9 [10,13,16], the apnea/hypopnea index (AHI) greater than 5 [9,11,14] or the high risk of obstructive sleep apnea, according to the Berlin sleep questionnaire [15]. Although, in one study the choice described as the "presence of OSA" for Nicola J. Adderley is unspecific [12]. In consensus, obstructive sleep apnea is defined as an AHI of 5 or greater with associated symptoms or an AHI of 15 or greater regardless of associated symptoms. Questionnaires or predictive models can be used, but those, although they have a high sensitivity (80% - 90%), have a low specificity (34%) for the detection of OSA [24].

The association of obstructive sleep apnea and atrial fibrillation can be explained by repetitive obstructive respiratory events that cause structural problems, myocardial remodeling, and damage through repetitive mechanical atrial distension, stretching of the atrial wall, and frequent episodes of atrial fibrillation. desaturation and resaturation of hemoglobin. Cyclic deoxygenation and reoxygenation are comparable to ischemia-reperfusion injury, increasing reactive oxygen species production, vascular inflammation, and blood pressure. In addition, the pronounced sympathetic activation that occurs toward the end of an obstructive episode is accompanied by vagally mediated bradycardia due to activation of the diving reflex. This sympathovagal activation likely induces acute electrophysiological arrhythmogenic changes and an increased frequency of premature atrial contractions, potentially initiating AF in a vulnerable individual [25].

The association of the degrees of severity of the OSA (mild, moderate, and severe) with AF can be questioned by studies where it is confirmed, such as that of Gemma Cadby *et al*. [26] or no significant association is found [27,28]. Further studies are needed to see the relationship in this topic.

The study has its limitations, such as the diverse selection according to the operational definition of obstructive sleep apnea among the studies, it is also a cross-sectional study, so there is no causal relationship between the factors.

CONCLUSIONS

In the present systematic review and meta-analysis, obstructive sleep apnea and atrial fibrillation were significantly associated. There is low heterogeneity between studies.

Further studies are recommended in the elderly population, especially over 80 years of age where the prevalence of atrial fibrillation is significant.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

The authors participated in the genesis of the idea, project design, data collection and interpretation, analysis of results, and preparation of the manuscript of this research paper.

FINANCING

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