










# Obstructive sleep apnea risk factor for chronic kidney disease: A systematic review and meta-analysis

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## ABSTRACT

**Introduction:** Obstructive sleep apnea (OSA) is related to chronic kidney disease (CKD), but its association is not fully understood.

**Objective:** To realize a systematic review with meta-analysis to determine the association between OSA and CKD.

**Methods:** Systematic review with meta-analysis of observational studies. The search was carried out in Embase, PubMed/Medline, Scopus, and Web of Science. The data were calculated by the hazard ratio (HR). The heterogeneity was identified by I squared.

**Results:** Five studies were included (n=6,710). The meta-analysis found an association between OSA and CKD (HR=2.00; confidence interval 95%=1.68-2.38).

**Conclusions:** We found an association between OSA and CKD.

**Keywords:** obstructive sleep apnea, chronic kidney disease, systematic review

## INTRODUCTION

Obstructive sleep apnea (OSA) referred to interrupted breathing in the upper respiratory tract during sleep for more than ten seconds due to obstruction in these pathways and increased sympathetic activity [1]. The absence of breath sounds is an alarming factor suggesting OSA's presence. In addition, patients also present drowsiness, headache, fatigue, and interrupted sleep as the most common symptoms [2]. Several studies have reported the high prevalence of OSA in hemodialysis patients; in this way, these patients have a prevalence ten times higher than healthy people [3].

Furthermore, chronic kidney disease (CKD) is a public health problem, especially in low- and middle-income countries, because it is one of the most important causes of morbidity and mortality and high global health costs [4]. CKD is one of the non-communicable chronic diseases whose prevalence has rapidly increased globally, between 1990 and 2017, the global mortality rate increased by 41.5% [5, 6]. In Peru, some studies estimate that the prevalence of CKD is between 1.0% and 18.0%, considering that no studies have been carried out in recent years related to changes in the prevalence or the trend in CKD mortality in the country [7].

The joint presence between OSA and CKD is directed towards cardiovascular complications among patients, with the last one, due to the constant drops in oxygen saturation

that can lead to an increase in oxidative stress that raises the risk of cardiovascular diseases [2, 8]. Besides, a series of studies have found that metabolic acidosis triggers the onset of OSA in patients with CKD. Still, there is no up-to-date evidence regarding the factors that link both pathologies. Therefore, for all ahead mentioned, in the present investigation, a systematic review with meta-analysis was carried out to determine the association between OSA and CKD.

## METHODS

Systematic review with meta-analysis of observational studies. This work used a search strategy using four databases: Embase, PubMed/Medline, Scopus, and Web of Science. The PRISMA statement was used as a guide for this manuscript.

### Inclusion & Exclusion Criteria

The studies that were included in this review met the following criteria to be part of this study:

- study had to be carried out in people over 18 years old,
- the age of the publication should not exceed 10 years, and
- the language of publication must be English or Spanish.

At the same time, the exclusion criteria were

- OSA diagnosis by the automatic report and

(b) CKD diagnosis by the automatic report.

### Selection of Studies

Rayyan software (<https://rayyan.qcri.org>) was used. The articles' titles and abstracts were reviewed by three researchers (GZZT, JAL-C, and LEMV-R). In case of discrepancy, they were resolved by a third investigator (VJV-P).

Then, the full text of all the included articles was reviewed. Then, in a Microsoft Excel 2019 sheet, it was placed whether the study should be included or not. This procedure was also carried out by three investigators (GZZT, JAL-C, and LEMV-R), and in the same way, if there were discrepancies, they were resolved by a third researcher (VJV-P).

### Data Extraction & Qualitative Analysis

The manuscripts that were selected went to data extraction, and a file prepared in Microsoft Excel 2019 was used. The information extracted from each article was the following: author, year, country, type of study, sample, a measure of the response variable, a measure of the exposure variable, and adjustment variables.

### Risk of Bias Assessment

Newcastle-Ottawa scale (NOS) for cohort studies were used to assess the quality of selected studies. GZZT, JAL-C, and LEMV-R were the ones that carried out the analysis. If any discrepancy occurred, it was resolved by VJV-P.

### Quantitative Analysis

The variables of interest for this review were worked on in a dichotomized manner. The independent variable was OSA,

classifying it as whether or not it was present in the participants, according to polysomnography. The dependent variable was CKD; it worked in the same way. These categorical data were expressed as hazard ratio (HR). The association measures were calculated with their respective 95% confidence interval (95% CI).

Heterogeneity was identified by I squared ( $I^2$ ), which was interpreted according to the Cochrane manual: 0.0% to 40.0%=it might not be important; 30.0% to 60.0%=may represent moderate heterogeneity; 50.0% to 90.0%=may represent substantial heterogeneity; 75.0% to 100%=considerable heterogeneity. Due to heterogeneity, a randomized model analysis was performed.

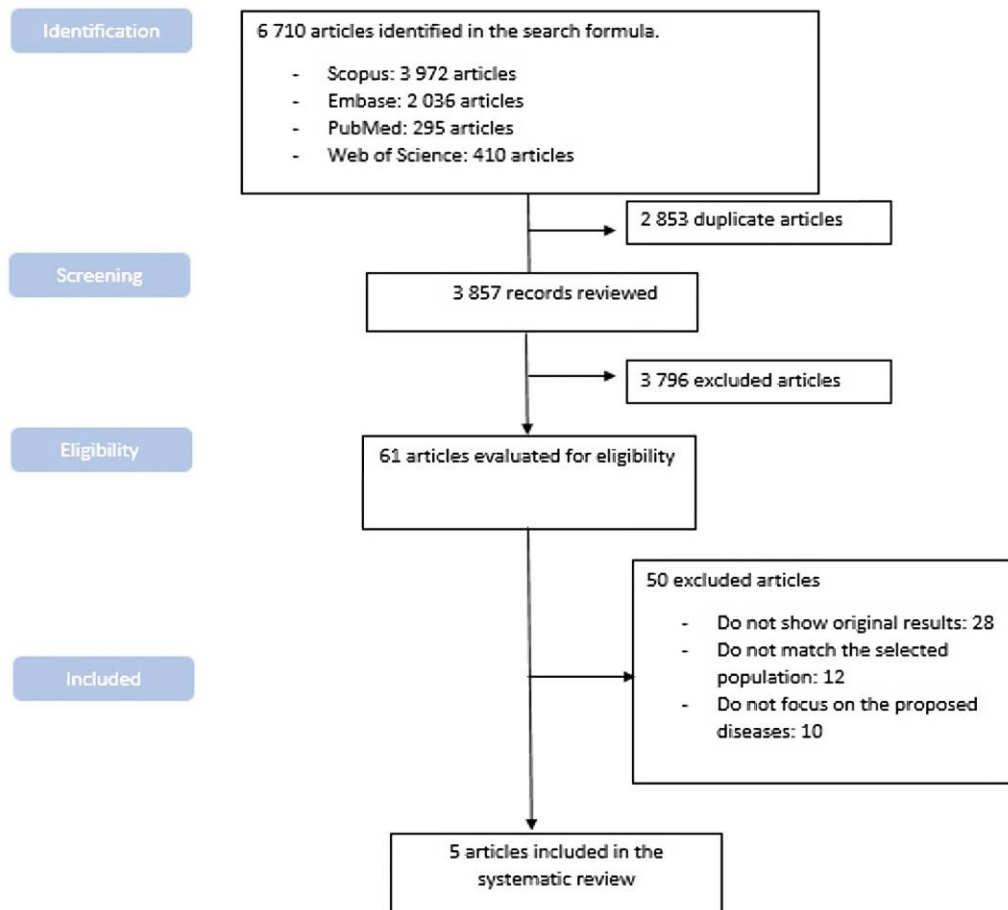
### Ethical Aspects

The manuscripts used to carry out this research were primary studies published in scientific journals, so the risks to the people who participated in the mentioned studies are minimal.

## RESULTS

### Eligible Studies

A total of 6,170 publications were identified. After eliminating duplicates (2,853), 3,857 articles were evaluated, considering title and abstract, excluding 3,796 manuscripts, and obtaining 61 full-text articles. Finally, when applying the selection criteria, five reports were obtained (**Figure 1**).



**Figure 1.** Flowchart of the study (Source: Authors' own elaboration)

**Table 1.** Evaluation of the quality of the studies using Newcastle-Ottawa scale

Reference	Selection			Comparability			Result			Score	Final judgement
	Representatives of exposed cohort	Selection of unexposed cohort	Determination of exposure	Outcome of interest was not present at start of study	There is a control (comparability) group	Study controls for any additional factors	Evaluation of result	Sufficient follow-up time	Adequacy of follow-up of cohorts		
[9]	★	★	★	★	★	★	★	★	★	8	Low-risk
[10]	★	★	★	★	★	★	★	★	★	8	Low-risk
[11]	★	★	★	★	★	★	★	★	★	8	Low-risk
[12]	★	★	★	★	★	★	★	★	★	8	Low-risk
[13]		★	★	★	★	★	★	★	★	7	Low-risk

**Table 2.** Characteristics & results of included studies on association between obstructive sleep apnea & chronic kidney disease

Reference	Year	Country	Design	Follow-up time	Sample size	Sex (% male)	Mean or median age	Type of sampling	Form of apnea diagnosis	Prevalence of apnea	Form of CKD diagnosis	Incidence of CKD	Measure of association	Adjustment variables
[9]	2015	USA	Cohort	2 years	3,079,514	93.00	61.0±14.0	N-P	P	0.75%	GFR<60 ml/min/1.73 m <sup>2</sup>	15.05%	HRa: 2.20 (CI 95%: 2.19-2.36)	Age, outcomes, race, marital status, & comorbidities
[10]	2015	Taiwan	Cohort	10 years	28,044	66.15	50.4±13.1 50.0±13.5	N-P	Coding ICD-9- CM	20.00%	Coding ICD-9- CM	1.30%	HRa: 1.94 (CI 95%: 1.52-2.46)	Age, location geography, income, urbanization, & comorbidities
[11]	2017	South Korea	Cohort	14 years	1,732	85.56	54 (48-60)	N-P	P	100%	GFR<60 ml/min/1.73 m <sup>2</sup>	0.75%	OR: 1.152 (CI 95%: 1.04-1.28)	Age, BMI, triglycerides, HDL cholesterol, postprandial glucose, & systolic blood pressure
[12]	2016	Taiwan	Cohort	10 years	43,434	62.80	46.6±14.9	N-P	Coding ICD-9- CM	20.46%	Coding ICD-9- CM	4.54%	HRa: 1.58 (CI 95%: 1.14-1.79)	Age, male sex, monthly income, urbanization, CCIS, comorbidities, & concomitant medications
[13]	2017	USA	Cohort	5 years	1,629	100	58.7±10.7	N-P	P	60.00%	GFR<60 ml/min/1.73 m <sup>2</sup>	11.00%	OR: 3.000 (CI 95%: 1.40-6.60)	Age, hypertension, obesity, smoking, & daily intake of NSAIDs

Note. N-P: Non-probabilistic; P: Polysomnography; CCIS: Charlson comorbidity index score

### Study Characteristics

Of the five included studies (n=3,154,353 approximately), whose samples were made up of 28,044 to 3,079,514 subjects. The included studies were cohort studies. CKD had an incidence of 0.75% to 15.05%. OSA was diagnosed by polysomnography in three studies. In contrast, others used the criteria of the international classification of diseases—clinical modification (9<sup>th</sup> revision) (ICD-9-CM). In contrast, two studies diagnosed CKD using ICD-9-CM criteria, and the glomerular filtration rate (GFR<60 ml/min/1.73 m<sup>2</sup>) was used in the rest.

### Risk of Bias Assessment

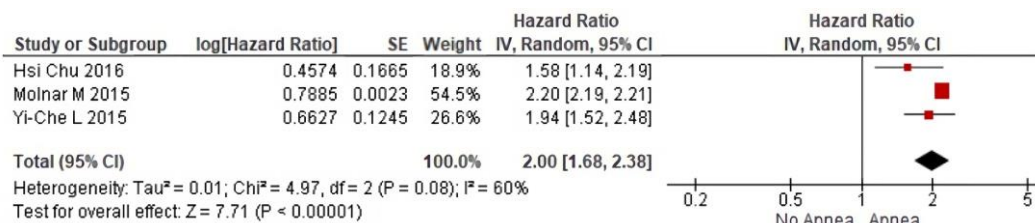
All selected studies were assessed using NOS for cohort studies. None of them established the comparability between the characteristics of the respondents and those who did not. All were of high quality and had low levels of bias (Table 1). Publication bias due to the small number of articles (less than 10) was not assessed. Complete results are shown in Table 2.

### Meta-Analysis for CKD Due to OSA

For the analysis of OSA and CKD, there are independently presented statistically significant associations like HR=1.58 and 95% CI=1.14-2.19, HR=2.20 and 95% CI=2.19-2.21, and HR=1.94 and 95% CI=1.52-2.48. A statistically significant association was found between both variables of interest (HR=2.00 and 95% CI=1.68-2.38) (Figure 2).

## DISCUSSION

A systematic review was carried out to determine whether OSA and CKD are associated. Although other systematic reviews have been carried out with the same variables of interest, none have performed a meta-analysis to search for the indicated association [14, 15]. The results obtained in this study regarding the association between the variables of interest contrast with the results presented by previous reviews.



**Figure 2.** Forest plot of random effects in chronic kidney disease according to presence of obstructive sleep apnea (Source: Authors' own elaboration)

The systematic review conducted in [14] concluded that OSA is dependently associated with CKD. In the same way, it was presented the same result concerning the association between both variables [15]. The number of studies found related to the association between OSA, CKD is less than the information found regarding other study variables [16, 17]. The studies that involve the Latin American population are minimal, even though this population is also vulnerable to CKD due to social, economic, and genetic factors [18].

The studies they selected were aimed at the adult population [11, 12, 18, 19]. Therefore, the behavior of these variables in children and the elderly is unknown. I feel that this last group is a vulnerable population for CKD [20]. The prevalence of OSA is 2.0% to 4.0% in children and is on the rise. In children, as in older adults, the pathophysiology is multifactorial, so timely detection and treatment are important [21-23].

OSA patients are at increased risk of developing cardiovascular and metabolic disease; decreased kidney function was associated with OSA with an increase of 20.0% to 40.0% in OSA patients [24, 25]. The prevalence of OSA is notably affected by the various diagnostic methods used, such as polysomnography or different questionnaires aimed at OSA. In various studies, a significant underestimation of the prevalence was shown in patients who were examined using questionnaires of OSA. Sleep demonstrates the low effectiveness of these tools [26].

These results can be explained by the chronic hypoxia hypothesis proposed by [27]. Several studies have shown a relationship between hypoxia and CKD mainly through mechanisms characterized by inflammation and microvascular insufficiency, tubulointerstitial fibrosis, and decreased renal function [28, 29]. Patients with OSA suffer from intermittent nocturnal hypoxia, which may play a key role as a risk factor for CKD in patients with OSA, causing a decrease in renal function [30]. The gradual development of CKD, including sympathetic activation, blood pressure swing, inflammation, and oxidative stress [31], hypoxemia can stimulate cytokine release and free radical production, leading to reduced nitric oxide and high levels of inflammatory proteins significantly linked to the severity of OSA and CKD [32, 33]. In a study, it was obtained as a result that patients with OSA have a five times greater risk of CKD, sex is an essential factor that affects the prevalence and clinical characteristics of the disease [34], and symptoms in female patients tend to be less severe, so they seek medical treatment later, resulting in more significant development of CKD [35].

Several studies have described that there is a greater risk of developing CKD in patients with OSA, considering differences in the study design, operational definitions of the variables, sociodemographic characteristics, and diagnostic methods for both CKD and OSA, which may explain the different results

shown by the evidence in the literature [13, 36]. OSA is independently associated with higher rates of adverse cardiac and cerebrovascular events, cardiovascular mortality, and myocardial infarction [37-39].

The objective of this systematic review was to establish the association between OSA and CKD. Articles, where the diagnostic methods were the same for both OSA and CKD were included, excluding articles that had unclear definitions or diagnostic methods. One of the strengths of this study was that we included studies with representative sample sizes. It should be noted that the association between OSA and CKD also seems to be bidirectional; that is, OSA can initiate the disease as CKD can also contribute to OSA, but this will depend on the comorbidities of the patients [1, 40].

The early detection and treatment of OSA in patients with CKD are of great importance for public health, taking each case individually and in a multidisciplinary manner, mainly by sleep medicine and nephrology.

## CONCLUSIONS

An association was found between OSA and CKD. Standardization of diagnostic methods is recommended for both OSA and CKD to avoid heterogeneous results. In addition, various strategies should be generated, considering the results of this manuscript, for the prevention and promotion of the health-related pathology in question.

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**Ethical statement:** The authors stated that the study was approved by the Research Ethics Committee of the Facultad de Medicina Humana de la Universidad Ricardo Palma. Written informed consents were obtained from the participants.

**Declaration of interest:** No conflict of interest is declared by authors.

**Data sharing statement:** Data supporting the findings and conclusions are available upon request from the corresponding author.

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