

Cardiovascular diseases in patients with obstructive sleep apnea: an integrative review

Doenças cardiovasculares em pacientes com apneia obstrutiva do sono: uma revisão integrativa

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ABSTRACT

Introduction: The objective of this review is to identify how obstructive sleep apnea (OSA) affects the development of cardiovascular diseases, increasing mortality rates. **Methods:** This is an integrative review of the literature, using studies from the last 20 years collected in the databases of PubMed, Google Scholar, LILACS and SciELO. **Results:** all selected articles associate obstructive sleep apnea to a higher risk of mortality from cardiovascular causes. **Conclusion:** Although there is an impact of genetic predisposition and lifestyle, repetitive upper airway obstruction during sleep caused by OSA is associated with increased cardiovascular risk.

Keywords: Obstructive sleep apnea; Cardiovascular diseases; Cardiovascular risk.

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Supporting sources:

None.

Conflicts of interest:

None.

Received on: March 8, 2025.

Approved on: October 6, 2025.

Publication Date: March 17, 2026.

DOI: 10.5935/2238-3182.2025e35208-en

RESUMO

Introdução: O objetivo desta revisão é identificar como a apneia obstrutiva do sono (AOS) afeta o desenvolvimento de doenças cardiovasculares, aumentando os índices de mortalidade. **Métodos:** Trata-se de uma revisão integrativa da literatura, utilizando-se estudos dos últimos 20 anos coletados nas bases de dados do PubMed, Google Acadêmico, LILACS e SciELO. **Resultados:** todos os artigos selecionados relacionam a apneia obstrutiva do sono a um maior risco de mortalidade por causas cardiovasculares. **Conclusão:** embora haja impacto da predisposição genética e do estilo de vida, a repetitiva obstrução das vias aéreas superiores durante o sono causada pela AOS está associada com o aumento do risco cardiovascular.

Palavras-chave: Apneia obstrutiva do sono; Doenças cardiovasculares; Risco cardiovascular.

INTRODUCTION

Obstructive sleep apnea (OSA) is a clinical condition characterized by repetitive complete or partial obstruction of the upper airways during sleep, resulting in periods of recurrent apnea, which may be accompanied by decreased oxygen saturation; when symptoms appear during the day, obstructive sleep apnea syndrome (OSAS) is characterized¹. This disorder is very frequent, although often undiagnosed, causing sleep fragmentation, deteriorating quality of life, and increasing cardiovascular risk. The diagnosis is made through nocturnal polysomnography, an exam that evaluates sleep efficiency².

Cardiovascular diseases are among the main causes of mortality in the world, corresponding to about 27% to 30% of deaths in Brazil, from 2000 to 2017, according to the Mortality Information System (SIM). In addition, these clinical conditions also cause loss of healthy years of life in those affected³. Among the cardiovascular diseases, the most alarming are the coronary and cerebral arteries, being caused mainly by atherosclerosis — plaques of fat and calcium inside these vessels —, and producing myocardial infarction and stroke. Changes in the heart rhythm, controlled by the autonomic nervous system, are also concerning, especially malignant arrhythmias.

Cardiovascular complications related to obstructive sleep apnea occur due to intermittent hypoxia, sleep fragmentation, oxidative stress, activation of the sympathetic nervous system, and increased intrathoracic pressure during obstructive events^{4,5}. The main ones are: changes in heart rate, arterial hypertension, cardiac arrhythmias, coronary artery disease, stroke, acute myocardial infarction, congestive heart failure, among others. Thus, the objective of this review is to address the relationship between this sleep disorder and the occurrence of cardiovascular events

from the pathophysiological point of view and to confirm whether there is an increase in mortality from this cause.

METHOD

This is an integrative review based on the literature published in the period 2003-2023, presenting a synthesis of varied studies.

The bibliographic research was carried out in the PubMed, Google Scholar, LILACS, and SciELO databases, between December 2022 and January 2023, based on the MeSH descriptors “Obstructive Sleep Apnea”, “Cardiovascular Diseases”, “Mortality” and their corresponding Portuguese terms, connected with the operator AND.

The following criteria were used to include the articles: articles published in Portuguese and English, published between 2005 and 2023, which addressed the theme of obstructive sleep apnea and cardiovascular morbidity and mortality, and with full text available free of charge. The exclusion criteria for the search were: duplicated studies, articles that did not address the topic, out of the established time frame, with age and sex restrictions, studies using animal models, case reports, and narrative reviews.

The three stages used for the selection of articles were: first, search in databases using the descriptors, the inclusion and exclusion criteria, in which 58 studies were found; second, reading of the titles and abstracts of the articles, in which 18 studies that met the research criteria were selected; and third, full and critical reading of the previously selected articles, allowing the exclusion of studies that did not meet the objective of this review, remaining 11 publications. The flow diagram demonstrating the study selection process is shown in Figure 1.

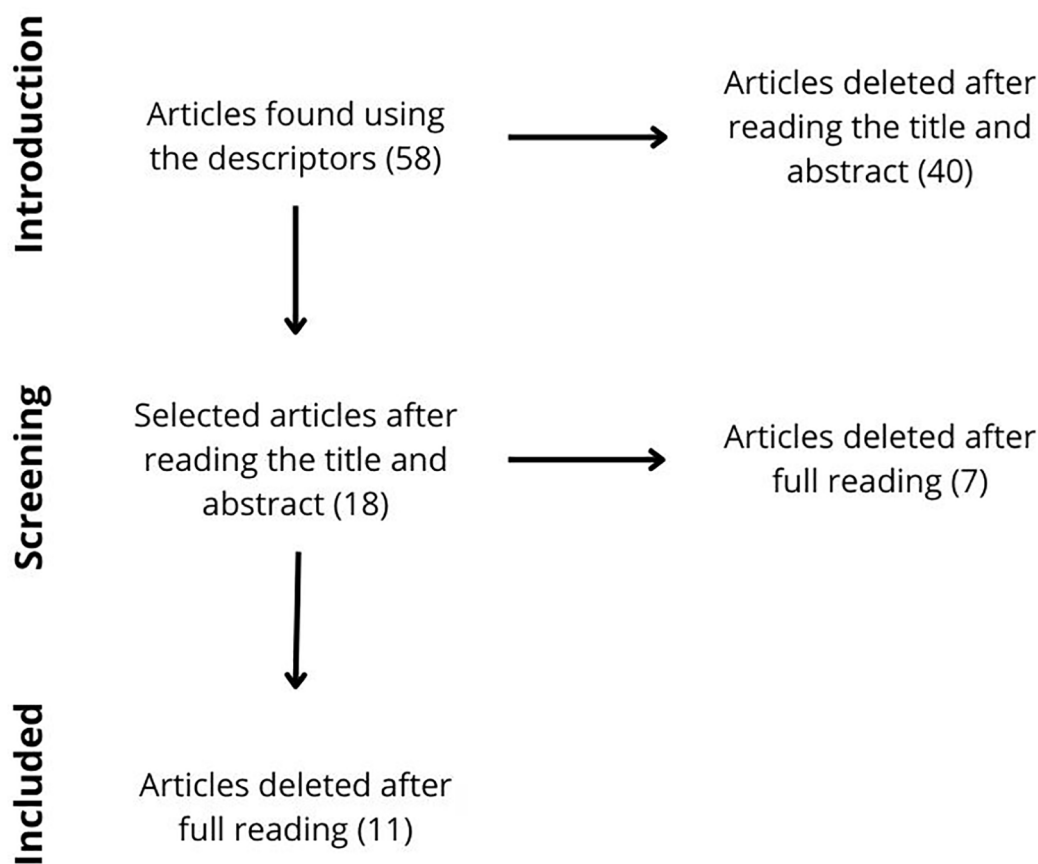


Figure 1. Flow diagram of the study. Source: Elaborated by the authors (2023).

The process of searching for articles resulted in the selection of broad and relevant works for the studied topic, they were able to promote a better understanding of the association between obstructive sleep apnea and cardiovascular events.

RESULTS

After reading the articles selected through the inclusion and exclusion criteria, it was possible to observe that 11 found some degree of relationship between obstructive sleep apnea and increased cardiovascular morbidity and mortality.

Table 1 organizes the essential information of the included studies: authors and year of publication, title, type of study, objective, and main conclusions.

DISCUSSION

The selected articles provide a relevant approach to the discussion, enabling the understanding of the

pathophysiological mechanisms of obstructive sleep apnea that lead to cardiovascular complications and, consequently, an increase in morbidity and mortality from these causes. Thus, it is worthwhile to present the main ideas developed by the studies, as well as their specificities.

Yoshihisa and Takeishi (2019)⁶ state that intermittent hypoxia leads to the activation of inflammation pathways and, consequently, to oxidative stress, in addition to oxyhemoglobin desaturation during the apnea phase with increased cardiac oxygen requirement, and therefore OSA is associated with myocardial damage and fluctuations in the heart stimulating complex. The authors also present that the decrease in intrathoracic pressure during apnea increases venous return to the right chambers of the heart, which can put pressure on the left ventricle and compromise its ejection; this oscillation causes an increase in sympathetic activity that causes susceptibility to increased blood pressure and heart rate in the phase that follows the event. In addition, oxidative stress, systemic inflammation, and sympathetic activation can cause endothelial dysfunction, favoring vascular complications.

Table 1. Brief summary of included study.

Author; Publication Year	Title	Study type	Objective	Main findings
Campostrini, D. D. A. (2014)	Obstructive Sleep Apnea Syndrome and Cardiovascular Diseases	Literature review	To present obstructive sleep apnea from a clinical and pathophysiological point of view, in addition to how it can be harmful to the cardiovascular system.	The diagnosis and treatment of obstructive sleep apnea are fundamental, mainly because OSA is a risk factor for cardiovascular diseases, which are currently the main causes of morbidity and mortality.
Drager, L. F. (2019)	Obstructive sleep apnea and cardiovascular diseases	Literature review	To discuss the association of OSA with cardiovascular diseases, and its treatment through continuous positive airway pressure (CPAP).	Obstructive sleep apnea may predispose to cardiovascular disease according to observational studies, but the previous presence of cardiovascular disease has not been proven to be a risk factor for OSA. More evidence is needed to understand the mechanisms that CPAP helps the treatment.
Floras, J. S. (2013)	Sleep apnea and cardiovascular risk	Literature review	Present the epidemiology, pathophysiology, and clinical implications of obstructive sleep apnea, as well as how it increases cardiovascular risk.	Some physicians minimize the mutual importance of obstructive sleep apnea in the pathogenesis of cardiovascular disease. Evidence indicates that OSA increases the chances of cardiovascular events, including death. In addition, it is necessary to study whether the treatment of OSA reduces the risk of these episodes.
Fonseca, M. I. P. (2014)	Death and Disability in Patients with Sleep Apnea - A Meta-analysis	Systematic review and meta-analysis	To investigate whether obstructive sleep apnea increases mortality and how it affects morbidity in relation to cardiovascular disease.	Obstructive sleep apnea increases the incidence of cardiovascular events and the length of hospital stay in these patients. In addition, treatment is able to reduce the occurrence of these episodes.
Lorenzi Filho, G. (2010)	Cardiovascular consequences of obstructive sleep apnea syndrome	Literature review	To analyze the mechanisms that explain the causal relationship between obstructive sleep apnea and cardiovascular diseases.	Obstructive sleep apnea can impact the cardiovascular system through activation of the sympathetic nervous system, systemic inflammation, insulin resistance and the production of oxidative stress.
Author; Publication Year	Title	Study type	Objective	Main findings
Mehra, R. (2019)	Obstructive sleep apnea and cardiovascular disease in adults	Literature review	To review and assemble the available evidence on OSA, relating its pathophysiology and cardiovascular events.	OSA is a significant risk factor for cardiovascular diseases, including hypertension, coronary heart disease, atrial fibrillation, and its association is related to higher morbidity and mortality.

continue...

... continued Table 1

Author; Publication Year	Title	Study type	Objective	Main findings
Pedrosa, R. P. (2008)	Obstructive sleep apnea syndrome and cardiovascular disease	Literature review	To review the physiology and pathology of OSA and its relation with obesity and pathologies of the cardiovascular system.	Knowing the pathophysiology of OSAS is important to promote the appropriate treatment of patients with OSA. In addition, it is necessary to actively search for patients with this condition.
Somers, V. K. (2008)	Sleep apnea and cardiovascular disease	Systematic review	To highlight the relevance of studies and advances on the interactions between obstructive sleep apnea and cardiovascular diseases.	In the current scenario of cardiovascular disease prevalence, there may be an increase in obstructive sleep apnea rates. The mechanisms by which OSA causes deleterious effects on the cardiovascular system are not yet fully understood. Thus, further studies among cardiovascular and sleep professionals are needed to promote improvement in the quality of life of these patients.
Yaggi, H. K. (2005)	Obstructive sleep apnea as a risk factor for stroke and death	Cohort study	To determine whether OSAS is related to the risk of stroke or death, removing other risk factors, such as hypertension.	The initial hypothesis of a relationship between apnea and a higher risk of stroke and death was confirmed, since OSAS increases the risk of fatal and non-fatal cardiovascular complications.
Yeghiazarians, Y. (2021)	Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association	Scientific statement	To summarize the current evidence and to provide guidelines for healthcare professionals and patients on OSA and cardiovascular disease.	OSA is strongly associated with cardiovascular conditions, and increases mortality related to them. The disease is still little recognized and treated.
Yoshihisa, A. e Takeishi, Y. (2019)	Sleep Disordered Breathing and Cardiovascular Diseases	Revisão de literatura	To characterize and demonstrate the impacts of obstructive sleep apnea with cardiovascular complications.	Obstructive sleep apnea causes hypoxia and negative intrathoracic pressure, which are deleterious to the cardiovascular system. In addition, it is necessary to verify whether the treatment of OSA improves the prognosis of patients with OSA and cardiovascular diseases.

Source: Elaborated by the authors (2023).

Obstruction of the upper airways during sleep causes greater respiratory effort and decreased oxyhemoglobin saturation, which leads to activation of the sympathetic nervous system, resulting in increased heart rate, vascular resistance, and blood pressure, according to Campostrini (2014)⁷. The repetition of hypoxemia and reoxygenation during the night causes oxidative stress, currently pointed out as a factor for the emergence of cardiovascular diseases in patients with obstructive sleep apnea. The author also states that there is an increase in vasoconstrictors, such as endothelin-1, and a decrease in vasodilator factors, such as nitric oxide; this variation generates endothelial dysfunction, which contributes to vascular alterations.

According to Fonseca (2014)⁸, there is a relationship between obstructive sleep apnea and the risk of death from cardiovascular diseases, since the heart is exposed to hypoxia repeatedly, generating an increase in pre and afterload, sympathetic activity and endothelial dysfunction. The long-term permanence of these variations is harmful and possibly a factor for the occurrence of cardiovascular events. The author also presents hypertension as a cause of cardiac abnormalities and negative repercussions on the brain, such as stroke. In addition, alternations in the autonomic nervous system during apneic events can disturb the heart rhythm, which can progress to malignant arrhythmias and cause increased cardiovascular events, including sudden death due to arrhythmia.

Lorenzi Filho (2010)⁹ shows that hypoxia, sleep interruption, negative intrathoracic pressure and increased blood pressure during apneic episodes are responsible for causing cardiovascular complications in the long term. The studies pointed out show the relationships found between untreated apneic patients, mostly, and higher risk of stroke and acute myocardial infarction, since obstructive sleep apnea would favor the development of atherosclerosis, arterial stiffness and increased carotid intima-media thickness. In addition, the activation of the sympathetic system, the hyposensitivity of baroreceptors and the alteration in hydroelectrolyte homeostasis would collaborate with cyclical increases in blood pressure in these patients.

Airway obstruction causes negative intrathoracic pressure that, due to the increase in venous return of the systemic circulation, will cause a deviation of the interventricular septum, compromising the functioning of the left ventricle. In the condition of apnea, there is also a divergence between supply and demand of oxygen to the myocardium, stimulating the sympathetic system, which leads to oxidative stress, increased heart rate and blood pressure. In the long term, such alterations can cause arrhythmias, cardiac ischemia, hypertension, myocardial hypertrophy and endothelial dysfunction — which, in turn, can favor atherosclerosis¹⁰.

Somers (2008)¹¹ shows that the negative intrathoracic pressure generated is responsible for increasing the volume of blood in the atria, ventricles and aorta, which can compromise the functioning of the ventricles and hemodynamic stability, and can cause an increase in afterload and atrial size. The combination of recurrent hypoxia and sleep fragmentation stimulates mechanisms of systemic inflammation — by increasing plasma levels of C-reactive protein, cytokines and adhesion molecules — and oxidative stress.

Unlike what is expected in a healthy sleep, patients with OSAS do not have a drop in blood pressure due to the various episodes of apnea, which cause persistent sympathetic activation and, consequently, an increase in blood pressure, according to Pedrosa (2008)¹². This demonstrates an association between OSAS and arterial hypertension, in which the first can be a secondary cause of the other and also impair its treatment, even with the use of antihypertensive drugs. In addition, changes in sympathetic activation behavior are related to higher risks of sudden death from acute myocardial infarction and stroke.

Drager (2019)¹³ discusses the relationship between OSA and arrhythmias. In episodes of apnea, in which the absence of ventilation causes hypoxemia (low level of oxygen in the blood), bradycardia occurs, which is followed by tachycardia as ventilation is reestablished, due to vagal

stimulation. Atrial fibrillation, which is responsible for significant morbidity and mortality, is present with greater recurrence in patients with OSA when compared to the general population. In addition, the author associated the syndrome with the occurrence of stroke, since both of them involve mechanisms of transient reduction in oxygen flow, inflammation cascades, oxidative stress, and excitotoxicity.

An observational cohort study with 1002 patients, of which 697 had OSAS, was developed by Yaggi (2005)¹⁴. In it, patients went through polysomnography and continued to be followed up to verify future events, such as cardiovascular accidents and deaths. It was detected that among individuals with OSAS there were higher rates of diabetes mellitus, hypertension and obesity when compared to the other participants in the study, in addition to the fact that sleep apnea is independently associated with stroke and death, confirming that the syndrome is prevalent in more than 60% of stroke patients, compared to 4% among the general adult population.

Evidence linking severe obstructive sleep apnea to coronary heart disease, regardless of other shared risks, has been described by Mehra (2019)¹⁵. This happens because OSA is related to low-grade myocardial injury, hypertension, increased homocysteine, decreased HDL, increased C-reactive protein, among other risk factors. In addition, it is noteworthy that the risk of developing atrial fibrillation in patients with OSA is four times more likely to occur, due to autonomic dysfunction, hypoxia, and higher negative intrathoracic pressure.

The pathophysiology of obstructive sleep apnea is described as: hypoxemia/reoxygenation, dysautonomia (failure of the autonomic nervous system), sleep disturbance, changes in intrathoracic pressure, and hypercapnia (increase in the partial pressure of carbon dioxide in the blood). These processes can trigger inflammation, hypercoagulability, metabolic dysregulation, hemodynamic changes, left atrial enlargement, and sympathetic activation, which are risk factors for the development of hypertension, atrial fibrillation, heart failure, coronary artery disease, stroke, and mortality¹⁶.

CONCLUSIONS

The association between obstructive sleep apnea (OSA) and cardiovascular morbidity and mortality was unanimous among the articles analyzed. From this literature review, it was possible to conclude that multiple effects of upper airway obstruction during sleep are associated with increased cardiovascular risk.

However, despite the evidence of the influence of obstructive sleep apnea on cardiovascular morbidity and

mortality, it is known that the genetic predisposition and lifestyle of individuals are also very relevant factors.

Finally, the importance of the active search, diagnosis of OSA by health professionals, and appropriate treatment, is emphasized, so that the mortality risks related to cardiovascular diseases associated with this syndrome and described in this study can be mitigated or even avoided.

AUTHOR'S CONTRIBUTIONS

We describe contributions to the papers using the taxonomy (CRediT) provided above:

Conceptualization, Investigation, Methodology, Visualization & Writing – original draft: BGO Dias; AJF da Silva e Silva; BR da Silva; GQN Baldani; J de O Machado; JL Ferreira. *Project administration, Supervision & Writing – review & editing:* EA Soares; F da Ré Guerra.

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