Death and Disability in Patients with Sleep Apnea – A Meta-analysis

Maria Inês Pires Fonseca, Telmo Pereira and Paulo Caseiro
Instituto Politécnico de Coimbra – ESTESC – Departamento de Fisiologia Clínica, Coimbra – Portugal

Abstract

Background: Several studies have been attempting to ascertain the risks of Sleep Apnea Syndrome (SAS) and its morbidity and mortality.

Objective: The main objective was to verify whether SAS increases the risk of death; the secondary objective was to evaluate its morbidity in relation to cardiovascular disease and the number of days hospitalized.

Methods: A systematic review and a meta-analysis were performed of the published literature. The research focused on studies comparing the number of deaths in patients with untreated SAS and in patients with non-SAS.

Results: The meta-analysis was based on 13 articles, corresponding to a total of 13394 participants divided into two groups (non-SAS = 6631; SAS = 6763). The meta-analysis revealed a clear association of SAS with the occurrence of fatal events, where the presence of SAS corresponded to a 61% higher risk of total mortality (OR=1.61; CI: 1.43 – 1.81; p < 0.00001), while the risk of death from cardiac causes was 2.52 times higher in these patients (OR = 2.52; IC: 1.80 – 3.52; p < 0.00001). Similar results were obtained for mortality from other causes (OR = 1.68; CI: 1.08 – 2.61; p = 0.02). Resembling results were obtained in the remaining outcomes: non-fatal cardiovascular events were higher in the SAS group (OR = 2.46; IC: 1.80 – 3.36; p < 0.00001), the average number of days hospitalized was also higher in the SAS group (IV = 18.09; IC: 13.34 – 22.84; p < 0.00001).

Conclusion: The results show that untreated SAS significantly increases the risk of death, cardiovascular events and the average number of days hospitalized. (Arq Bras Cardiol. 2015; 104(1):58-66)

Keywords: Sleep Apnea Syndromes / mortality; Sleep Disorders / mortality; Death, Sudden, Cardiac.

Introduction

The high prevalence and wide spectrum of severity of sleep-disordered breathing are well documented in several studies. Although the methodology varies, these studies demonstrate a similar prevalence (approximately 6%). By analyzing this data by gender this value is higher among men1-3.

According to a new update in the Wisconsin Sleep Cohort Study, for a population with mild to severe disordered breathing, the prevalence is 10 % in men, and 3% in women between the ages of 30-49, and 9% in women between the ages of 50-704. Although this high prevalence, there’s been a report that almost 75% of this population is undiagnosed. It is also known that this syndrome contributes to an increase rate in morbidity and in mortality5,3.

Cardiovascular diseases are associated with SAS and its incidence is 2 to 3 times higher in cardiovascular patients. Moreover, it’s estimated that this value tends to increase because obesity (SAS main risk factor) is exponentially increasing in the population5-4.

In patients with acute Myocardial Infarction (MI), SAS can be present and it’s related with death. It’s believed that the mechanism behind cardiovascular death during sleep is nocturnal hypoxia5.

According to the Apnea-Hypopnea Index (AHI) or according to the Respiratory disturbance Index (RDI), sleep apnea can be classified as mild, moderate or severe. According to several authors5-8, the RDI/AHI is rated: Mild - 5 to 15 events per hour; Moderate - 15 to 30 events per hour; Severe - ≥ 30 events per hour. Evidence exists that demonstrates higher overall risk according to increasing RDI/AHI ratings5,3.

Evidence from clinical studies revealed that patients with non-treated SAS have a higher death risk comparing to patients with treatment5. There are several methods of treatment such as noninvasive ventilation, oral prostheses, surgical procedures, pharmacological therapies and sleep hygiene5-14.

In order to confirm the impact of SAS in the population and its relation to major cardiovascular events, we decided to make a meta-analysis of the public literature, which the aim was to verify if SAS increases the risk of death, CV events and time of hospitalizations.
Methods

Study Design

A systematic review and meta-analysis of the published literature addressing the mortality and morbidity related to SAS was performed. The methodology was based on the guidelines of the PRISMA group (preferred reporting items for systematic reviews and meta-analyses)15.

Research Strategy

The predefined outcomes were: global death, cardiovascular death (CV death), death from other causes, cardiovascular events (CV events) and hospitalizations. The inclusion criteria were: SAS populations, adults, with no treatment, the articles needed to be written in English, published in journals and required to evaluate at least one of the final outcomes. All studies that failed any of the predefined criteria were excluded.

The evaluation of inclusion criteria was made by two researchers and conducted independently, without any exchange of information among researchers (blind critical review).

The literature search was performed in the PUBMED, EMBASE and SCIELO databases, and only articles published from the year 2002 forward were considered.

Selection of studies

The selection of articles was based on a standardized form, which was rated independently by the two reviewers, who classified the articles according to the title, abstract or full text. When the title and summary of the studies did not contain the necessary information to complete the form, they were referred to a complete review.

Firstly, a search was made based on keywords (Sleep apnea AND death/mortality; Sleep breathing disorders AND death/mortality; Sleep disorder breathing AND sudden death NOT sudden infant death; Sleep apnea AND sudden death NOT sudden infant death). After this research, a total of 427 articles were found that met the predefined characteristics.

At the end of the independent review, the two reviewers met with the aim of resolving disagreements arising from the rating for inclusion or exclusion of studies. This meeting resulted in the total number of articles to be included in the study (Figure 1).

Statistical analysis

The statistical analysis was performed using the Methodology Review, of the statistical software Review Manager Version 5.15.

Regarding the type of analysis (random/fixed), it was decided according to the homogeneity or heterogeneity of the sample. For a homogeneous sample an analysis of fixed effects was conducted and a random effects analysis was done for heterogeneous samples. Heterogeneity was assessed by the Cochrane Q test and complemented with I² (which indicates the proportion of variability between studies, providing a measure of heterogeneity). We considered the sample was homogeneous for a value of p ≥ 0.05 in Q test and I² value of ≤ 25%.

The overall effects of the analysis were tested with the Z-Test, and the odds ratio (OR) and the Mean Difference, with 95% confidence intervals (CI), were extracted for dichotomous outcomes and continuous outcomes respectively. Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as absolute frequencies. The criterion for statistical significance was p ≤ 0.05 for a 95% CI. The funnel plot was used to detect eventual publication bias (Y-axis – Study weight or sample size; X-axis – Study weight or sample size; X-axis – hazard ratio).

Results

Sample Characterization

A total of 14 articles were included in this meta-analysis, 11 of these articles assessed the global mortality, 7 evaluated CV deaths, 4 studied deaths from other causes, 5 analyzed CV events and 2 studies examined time of hospitalizations, in days.

For the purposes of this meta-analysis, all studies that contained more than a group of individuals divided by AHI/ RDI/ODI (Oxigene Dessaturation Index) were reduced to 2 groups (the group without SAS and the group with SAS). All patients on CPAP (for more than 2 months) were excluded from this meta-analysis. The SAS group includes patients with OSA (Obstructive Sleep Apnea) and patients with CSA (Central Sleep Apnea). Plus, in the control group were included patients without SAS and with mild SAS depending on the characteristics of each study.

In Table 1, the final characterization of our sample is represented which includes clinical characteristics and final outcomes.

SAS and Total Mortality

When data from all studies that assessed total mortality were pooled using the fixed model analysis there was a significant overall effect, the SAS group expressed an increased risk of death from any cause (OR = 1.66; CI: 1.48–1.86; p < 0.00001). The analysis of Heterogeneity reveals a heterogenic sample, although the value of p = 0.08 for Q test, the I² = 41% is above 25%.

To minimize the effect of heterogeneity we conducted a random-effects analysis (Figure 2). As it can be seen, in this analysis the group with SAS maintains a higher association with the occurrence of death from any cause, with an OR of 1.94 (CI: 1.52 – 2.47; p < 0.00001). However, the funnel plot analysis allowed the identification of an important asymmetry, since there are two studies which clearly diverge from the overall pattern.

According to the Masuda et al24 and Sahlin et al21 CI (Figure 2), a greater difference between CI values can be seen from this two studies comparing to estimated CI value (Masuda et al24 – CI: 1.97 – 15.78; Sahlin et al21 – CI: 1.56 – 95.34; estimated CI: 1.52 – 2.47), which can lead to a publication bias. Therefore, we decided to conduct a sensitivity complementary analysis. To this end, we replicated the meta-analysis after excluding these two
Fonseca et al.  
Death and disability in patients with sleep apnea  

**Original Article**

| Identification | Records identified through database searching (n = 338) | Additional records identified through other sources (n = 89) |
|----------------|--------------------------------------------------------|----------------------------------------------------------|
|                | Records after duplicates removed (n = 104)             |                                                          |
|                | Records excluded (n = 260) By title - 214 By abstract - 47 |
|                | Records screened (n = 323)                              |                                                          |
|                | Full-text articles assessed for eligibility (n = 63)    |                                                          |
|                | Full-text articles excluded (n = 49)                    |                                                          |
|                | Studies included in qualitative synthesis (n = 14)      |                                                          |
|                | Studies included in quantitative synthesis (meta-analysis) (n = 14) |

**Figure 1 – Process of selection of studies.**

studies (Masuda et al.²⁴ and Sahlin et al.⁵). A significant association of SAS with death from all causes persisted, with an OR value of 1.61 (CI: 1.43 – 1.81; p < 0.00001), followed by an absence of heterogeneity, according to the Q test analysis (p = 0.44) and to a $I^2 = 0\%$ (Figure 3).

**SAS and Cardiovascular Mortality**

The analysis of the outcome "CV deaths" identified a significant association of SAS with the occurrence of the event (Figure 4) with an OR value of 2.52 (CI: 1.80 – 3.52; p < 0.00001), and absence of heterogeneity (p = 0.78 and $I^2 = 0\%$). Concerning sample symmetry, the funnel plot analysis indicated a clear symmetry, reinforcing the validity of the estimate association extracted from this analysis.

**SAS and Mortality from other causes**

To evaluate death from other causes (Non-Cardiovascular death), we once again proceed to a fixed analysis, represented on Figure 5. As shown, the SAS group shows a higher risk comparing to the non-SAS group, representing a 68% higher risk of death from other causes in patients with SAS (OR = 1.68; CI: 1.08 – 2.61; p = 0.02). There was no significant heterogeneity effects (p = 0.50 and $I^2 = 0\%$). The funnel plot did not identify any significant deviation from the general pattern of the sample.

**SAS and Hospitalizations**

The analysis concerning the “Hospitalizations” Outcome is depicted Figure 6. The fixed effects analysis applied to
Table 1 – Final characterization and final outcomes (SAS – Sleep Apnea Syndrome)

|                        | Total per group |             |
|------------------------|-----------------|-------------|
|                        | Non-SAS         | SAS         | Total        |
| Sample (n)             | 6631            | 6763        | 13394        |
| Age (M/σ)              | 61.5 ± 8.2      | 64.4 ± 7.9  | 62.9 ± 8.0   |
| Women (n/%)            | 3447 (51.9%)    | 1980 (29.3%)| 5427 (40.5%) |
| Men (n/%)              | 3184 (48.0%)    | 4783 (70.7%)| 7967 (59.5%) |
| Hypertension (n/%)     | 2724 (41.0%)    | 3468 (51.3%)| 6192 (46.2%) |
| Diabetics (n/%)        | 563 (8.5%)      | 1003 (14.8%)| 1566 (11.7%) |
| CV diseases (n/%)      | 946 (14.3%)     | 1239 (18.3%)| 2185 (16.3%) |
| Follow Up (years)      | 6.1             | 6.1         | 6.1          |
| BMI (M/σ)              | 27 ± 3.7        | 29.4 ± 4.2  | 28.2 ± 3.9   |
| AHI/RDI/ODI (M/σ)      | 4.4 ± 2.7       | 29.2 ± 8.73 | 16.8 ± 5.7   |
| Epworth Sleep Scale (M/σ)| 7.3 ± 3.2   | 8.6 ± 3.0   | 7.9 ± 3.1    |
| Global Mortality       | 711 (10.7%)     | 896 (13.2%) | 1607 (12%)   |
| CV death               | 65 (0.98%)      | 182 (2.7%)  | 247 (1.8%)   |
| Death from other Causes| 49 (0.73%)      | 52 (0.77%)  | 101 (0.75%)  |
| Hospitalizations       | 44 (0.66%)      | 78 (1.2%)   | 122 (0.91%)  |
| CV events              | 68 (1%)         | 262 (3.9%)  | 330 (2.5%)   |

CV diseases: Cardiovascular diseases; BMI: Body Mass Index; AHI: apnea hypopnea index; RDI: Respiratory disturbances index; ODI: oxygen desaturation index; CV death: cardiovascular death; CV events: Cardiovascular events; SAS: Sleep apnea syndrome.

Figure 2 – Mortality Outcome – Random-effects analysis (Odds Ratio)

The average in-hospital days, demonstrated longer stays in hospital in the SAS group comparing to the non-SAS group, with a mean difference of 18.09 days (IC: 13.34 – 22.84; p < 0.00001). In other words, the SAS patients are hospitalized, in average, 18.09 days more than the non-SAS patients. Regarding the sample heterogeneity and symmetry, we found a p = 0.55 in the Q Test and an I² = 0%, plus a symmetric distribution in the funnel plot.
**Figure 3** – Sensitivity analysis – Fixed Analysis

Turkington et al\(^1\); Yaggy et al\(^2\); Marshall et al\(^3\); Sahlin et al\(^4\); Young et al\(^5\); Valham et al\(^6\); Punjabi et al\(^7\); Martínez-García et al\(^8\); Yumino et al\(^9\); Masuda et al\(^10\).

| Study or Subgroup | SAS | Non-SAS | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|-----|---------|--------|-----------------------------|-----------------------------|
| HADER 2006        | 3   | 8       | 11     | 0.4%                        | 2.45 [0.51, 11.87]          |
| MARSHAL 2008      | 11  | 95      | 22     | 2.2%                        | 1.57 [0.73, 3.36]           |
| MARTINEZ-GARCIA 2009 | 58  | 107     | 11     | 1.7%                        | 2.15 [0.94, 4.93]           |
| MASUDA 2011       | 19  | 44      | 6      | 5.0%                        | 5.57 [1.97, 15.78]          |
| SAHLIN 2008       | 52  | 53      | 64     | 0.0%                        | 12.19 [1.56, 95.34]         |
| TURKINGTON 2004   | 33  | 73      | 12     | 1.8%                        | 2.41 [1.08, 5.36]           |
| VALHAM 2008       | 46  | 211     | 34     | 6.4%                        | 1.21 [0.73, 1.98]           |
| YAGGY 2005        | 50  | 697     | 14     | 3.9%                        | 1.72 [0.93, 3.15]           |
| YOUNG 2008        | 34  | 365     | 46     | 4.4%                        | 2.48 [1.57, 3.93]           |
| YUMINO 2009       | 20  | 80      | 14     | 1.9%                        | 2.36 [1.11, 5.01]           |

Total (95% CI) 4501 5624 100.0% 1.61 [1.43, 1.81]

Total events: 825 641

Heterogeneity: Chi\(^2\) = 7.91, df = 8 (P = 0.44); I\(^2\) = 0%

Test for overall effect: Z = 8.07 (P < 0.00001)

**Figure 4** – CV death Outcome – Fixed Analysis (Odds Ratio)

Marin et al\(^1\); Young et al\(^2\); Martínez-García et al\(^3\); Yumino et al\(^4\); Shah et al\(^5\); Masuda et al\(^6\); Sano et al\(^7\).

| Study or Subgroup | SAS | Non-SAS | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|-----|---------|--------|-----------------------------|-----------------------------|
| MARIN 2005        | 60  | 1015    | 8      | 24.4%                       | 2.01 [0.95, 4.26]           |
| MARTINEZ-GARCIA 2009 | 37  | 107     | 6      | 12.4%                       | 2.20 [0.83, 5.84]           |
| MASUDA 2011       | 14  | 44      | 4      | 5.2%                        | 5.37 [1.61, 17.86]          |
| SANO 2013         | 20  | 89      | 10     | 15.8%                       | 2.29 [1.00, 5.22]           |
| SHAH 2010         | 33  | 1024    | 7      | 19.7%                       | 1.93 [0.85, 4.39]           |
| YOUNG 2008        | 13  | 365     | 12     | 11.3%                       | 3.52 [1.59, 7.70]           |
| YUMINO 2009       | 15  | 80      | 8      | 11.0%                       | 3.03 [1.22, 7.54]           |

Total (95% CI) 2724 2116 100.0% 2.52 [1.80, 3.52]

Total events: 192 55

Heterogeneity: Chi\(^2\) = 3.24, df = 6 (P = 0.78); I\(^2\) = 0%

Test for overall effect: Z = 5.41 (P < 0.00001)

**Figure 5** – Death from other causes Outcome – Fixed Analysis (Odds Ratio)

Young et al\(^2\); Martínez-García et al\(^3\); Yumino et al\(^4\); Masuda et al\(^6\).

| Study or Subgroup | SAS | Non-SAS | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|-----|---------|--------|-----------------------------|-----------------------------|
| MARTINEZ-GARCIA 2009 | 21  | 107     | 5      | 21.1%                       | 1.27 [0.44, 3.70]           |
| MASUDA 2011       | 5   | 44      | 2      | 5.6%                        | 3.08 [0.57, 16.73]          |
| YOUNG 2008        | 21  | 365     | 34     | 52.1%                       | 2.02 [1.15, 3.52]           |
| YUMINO 2009       | 5   | 80      | 8      | 21.1%                       | 0.88 [0.28, 2.78]           |

Total (95% CI) 596 1351 100.0% 1.68 [1.08, 2.61]

Total events: 52 49

Heterogeneity: Chi\(^2\) = 2.39, df = 3 (P = 0.59); I\(^2\) = 0%

Test for overall effect: Z = 2.30 (P = 0.02)
SAS and Non-Fatal Cardiovascular Events

Finally, for “CV events” Outcome, once again we proceed to a fixed analysis (Figure 7). A significant association between SAS and the risk of non-fatal CV events was also found, with the SAS group presenting a 2.46 higher risk comparing to the non-SAS group (OR = 2.46; CI: 1.80 – 3.36; p < 0.00001). There was no significant heterogeneity (p = 0.66; I² = 0%), and the funnel plot exposed a symmetric distribution of the sample.

Discussion

Given the results reported, a clear association was shown between SAS and the risk of death, cardiovascular diseases and the number of days hospitalized. This association is certainly related to the pathophysiology of SAS.

The SAS exposes the heart to an intermittent hypoxia, which may result in an increased pre-load and after-load, in an increased sympathetic activity and in endothelial dysfunction1,28-33. The constant presence of these changes is detrimental in long-term, which might be the reason for cardiovascular events, fatalities and the increased number of days hospitalized in these patients.

The number of days hospitalized probably reflects a greater number of peri-hospital complications and a generally slower recovery from several clinical illnesses, which, moreover, may also be more severe.

The death from other causes (cancer, tumors, infections, accidents/suicide, and other unknown causes) was superior in patients with SAS. This relation may lie in the fact that most of these patients are obese, diabetic or hypertensive, which leads to a greater vulnerability of the organism, being more susceptible to cancer development and the emergence of infections. However, road accidents in patients with SAS are very common as EDS decreases alertness while driving and falling asleep at the wheel sometimes causes fatal accidents.

Hypertension is responsible for many cardiac abnormalities and has a negative impact on the brain, with a well-known relation between high blood pressure and stroke1,31. The presence of cardiac arrhythmias may also be responsible for increased cardiovascular events and even arrhythmic sudden death. Variations in the autonomous nervous system during apneas cause changes in heart rhythm that might degenerate into malignant arrhythmias32. Furthermore, acute MI is also highly prevalent in patients with SAS, being either a cause or a consequence of SAS19. This may also contribute to an increased number of fatal and non-fatal events in patients with SAS.
On the other hand, cardiovascular events and fatalities have an economic impact on the population. The increase in hospital admissions results in more costly hospitalizations; comorbidities require additional expenses associated with pharmacological treatments or with other types of therapies and result in a detrimental effect on the quality of life of the patients. Death has a negative impact on the family and also reduces their future income.

**Study Limitations**

Study populations were different, there were some studies that evaluated patients with diseases [Martínez-García et al.]; Sahlin et al.; Valham et al.; Sano et al.; Masuda et al.; Yumino et al.; Turkington et al.; Hader et al.], other studies have evaluated patients with SAS symptoms [Marin et al.; Yaggy et al.; Shah et al.], which may contribute to an increased risk of events. One study was based on Sleep Heart Health Study, which comprises a database of patients of various studies, like Framingham Offspring and Omni Study, The Atherosclerosis Risk in Communities Study, The Cardiovascular Health Study, The Strong Heart Study and other Cohort studies.

Furthermore, it is worth noting the fact that we only worked with two groups (SAS and non-SAS), not allowing us to conduct an analysis according to the severity of the disease. Although our sample had an average ≤ 5 events per hour in the control group, there were studies included that had a higher value of AHI/RDI/ODI [Martínez-García et al.; Sahlin et al.; AHI 0 – 9 events/hour; Sahlin et al.; AHI < 15 events/hour; Yumino et al.; AHI < 15 events/hour; Turkington et al.; RDI < 10 events/hour]. This fact may have contributed to some of the heterogeneity of the results, thus motivating the adoption of random effect analyzes, in some cases, supplemented with sensitivity analyzes. In addition, the fact that we excluded patients with treatment made it impossible to assess the treatment’s efficacy, although such was beyond the objective of this meta-analysis.

**Conclusions and Future Directions**

The aim of this report was answered in this meta-analysis. This meta-analysis reinforces previous investigation pointing that SAS increases the risk of death and cardiovascular events, and that SAS patients have longer stays in hospitals, than non-SAS patients.

Furthermore, our literature review indicates that treating these patients is very important. Several articles have been comparing non-treated patients with treated patients, and their results have shown the efficacy of the treatment in reducing the number of deaths and cardiovascular events. For further investigation, we think it’s important to make another meta-analysis evaluating non-treated SAS with treated SAS, and comparing the risk of death and cardiovascular events, and measuring the severity of this disease, since there are many reports showing the difference between moderate SAS and severe SAS.

We also believe that it is important to alert our health professionals to the risks of these diseases and its comorbidities. A plan must be considered, to implant new strategies in primary health care, to triage the affected population and to implant treatment measures, in order to reduce the impact of this disease.

**Author contributions**

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Fonseca MIP, Pereira T, Caseiro P; Statistical analysis: Fonseca MIP, Pereira T; Writing of the manuscript: Fonseca MIP.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**Sources of Funding**

There were no external funding sources for this study.

**Study Association**

This article is part of the thesis of master submitted by Maria Inês Pires Fonseca, from Instituto Politécnico de Coimbra.

**References**

1. Somers V, White D, Amin R, Abraham W, Costa F, Culebras A, et al; American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology; American Heart Association Stroke Council; American Heart Association Council on Cardiovascular Nursing; American College of Cardiology Foundation. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation. 2008;118(10):1080-111. Erratum: Circulation. 2009;119(12):e380.

2. Young T, Finn L, Peppard P, Seidlo-Coxe M, Austin D, Nieto F, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin Sleep Cohort Study. Sleep. 2008;31(8):1071-8.

3. Young T, Palta M, Dempsey J, Peppard P, Nieto J, Hla K. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort Study. WMJ. 2009;108(5):246-9.

4. Peppard P, Young T, Barnet J, Palta M, Hagen E, Hla K. Increased Prevalence of Sleep-Disordered Breathing in Adults. Am J Epidemiol. 2013; 177 (9): 1006 – 1014.

5. Sahlin C, Sandberg O, Gustafson Y, Bucht G, Carlberg B, Stenlund H, et al. Obstructive sleep apnea is a risk factor for death in patients with stroke. Arch Intern Med. 2008, 168(3):297-301.
6. Teixeira F. Distúrbios respiratórios obstrutivos do sono: síndrome de apneia-hipopneia obstrutiva do sono e síndrome da resistência das vias aéreas superiores. Rev Port Clin Geral. 2006;22:613-23.

7. Norman R, Scott M, Ayappa I, Walabhe J, Rapoport D. Sleep continuity measured by survival curve analysis. Sleep. 2006;29(12):1625-31.

8. Wink J. Sleep disorder breathing and mortality. Revista Factores de Risco. 2010;17(4):76-8.

9. Punjabi N, Caffo B, Goodwin J, Gottlieb D, Newman A, O’Connor G, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med. 2009;6(6):e1000132.

10. Berry R, Parish J, Hartte K. The use of auto-titrating continuous positive airway pressure for treatment of adult obstructive sleep apnea. Sleep. 2002;25(2):140-73.

11. Gay P, Weaver T, Loubé D, Iber C; Positive Airway Pressure Task Force; Standards of Practice Committee; American Academy of Sleep Medicine. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep. 2006;29(3):381-401.

12. Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D; et al; American Academy of Sleep Medicine. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep related breathing disorders. Sleep. 2006;29(3):375-80.

13. Gami AS, Olson Ej, Shen WK, Wright RS, Ballman KV, Hodge DO, et al. Obstructive sleep apnea an the risk of sudden cardiac death: a longitudinal study of 10,701 adults. J Am Coll Cardiol. 2013;62(7):610-6.

14. Morgenthaler TI, Gay PC, Gordon N, Brown JK. Adaptive servventilation versus noninvasive positive pressure ventilation for central, mixed, and complex sleep apnea syndromes. Sleep. 2007;30(4):468-75.

15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.

16. The Cochrane Collaboration. Review Manager (RevMan). [Computer programme, Version 5.1. Copenhagen: The Nordic Cochrane Centre; 2011.

17. Turkington PM, Allgar V, Barnford J, Wasklyn P, Elliott MW. Effect of upper airway obstruction in acute stroke on functional outcome at 6 months. Thorax. 2004;59(5):367-71.

18. Marin JM, Carrizo SJ, Vicent E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365(9464):1046-53.

19. Yaggi HK, Concato J, Kerman WN, Lichtman JH, Brill L, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. 2005;353(19):2034-41.

20. Hader C, Hunz M, Wele-Bart A, Raske K. Sleep Disordered Breathing in the Elderly: A Three Year Longitudinal Cohort Study. J Physiol Pharmacol. 2006;56 Suppl 4:119-29.

21. Marshal NS, Wong K, Liu P, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Brusselton Health Study. Sleep. 2008;31(8):1079-85.

22. Vallhav M, Moue T, Rabben T, Stenlund H, Wiklund U, Franklin KA. Increased risk of stroke in patients with coronary artery disease and sleep apnea: a 10 year follow-up. Circulation. 2008;118(9):955-60.

23. Martínez-García MA, Soler-Cataluñia JJ, Ejarque-Martínez L, Soriano Y, Román-Sánchez P, Illa FB, et al. Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke an obstructive sleep apnea: a 5-year follow-up study. Am J Respir Crit Care Med. 2009;180(1):36-41.

24. Yunino D, Wáng H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, et al. Relationship between sleep apnea and mortality in patients with ischaemic heart failure. Heart. 2009;95(10):819-24.

25. Masuda T, Murata M, Horoe S, Iwauy Y, Sasaki N, Ogura M, et al. Sleep-disorder breathing predicts cardiovascular events and mortality in hemodialysis patients. Nephrol Dial Transplant. 2011;26(7):2289-95.

26. Sano K, Watanabe E, Hayano J, Mieno Y, Sobue Y, Yamamoto M, et al. Central sleep apnea and inflammation are independently associated with arrhythmia in patients with heart failure. Eur J Heart Fail. 2013;15(9):1003-10.

27. Shah N, Yaggi H, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. Sleep Breath. 2010;14(2):131-6.

28. Bradley TD, Flora JS. Sleep apnea and heart failure: Part II: central sleep apnea. Circulation. 2003;107(13):1822-6.

29. Bradley TD, Flora JS. Sleep apnea and heart failure: Part I: obstructive sleep apnea. Circulation. 2003;107(12):1671-8.

30. Gami AS, Somers VK. Implications of obstructive sleep apnea for atrial fibrillation and sudden cardiac death. J Cardiovasc Electrophysiol. 2008;19(9):997-1003.

31. Barreto-Filho J, Jesus E. Síndrome da apneia obstrutiva do sono e risco cardiovascular. Revista Factores de Risco. 2010;17(4):20-6.

32. Wiegert GT, Faria DG, Castanho LA, Dias PA, Greco OT. Apnéia obstrutiva do sono e arritmias. Relampa. 2010;23(1):5-11.

33. Jilek C, Krenn M, Sebah D, Obermeier R, Braune A, Kohl V, et al. Prognostic impact of sleep disordered breathing and its treatment in heart failure: an observational study. Eur J Heart Fail. 2011;13(11):68-75.

34. Gottlieb DJ, Yenokyan G, Newman AB, O’Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010;122(4):352-60.

35. Millenon O, Pillière R, Foucher A, de Roquefeuil F, Aegerter P, Jondeau G, et al. Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study. Eur Heart J. 2004;25(9):728-34.

36. Campos-Rodrigues F, Peña-Gríñan N, Reyes-Nuñez N, De la Cruz-Moron SF, et al. Prospective study of obstructive sleep apneoa and incidental coronary heart failure and heart failure: the sleep heart health study. Circulation. 2010;122(4):352-60.

37. Doherty LS, Kiely JL, Swan V, McNicholas WT. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. J Cardiovasc Electrophysiol. 2008;19(9):997-1003.

38. Shah N, Yaggi H, Concato J, Mohsenin V. Obstructive sleep apnea as an independent risk factor for cardiovascular disease and death. J Cardiovasc Electrophysiol. 2003;14(2):131-6.

39. Kasai T, Noni K, Dohi T, Yamagisawa N, Ishiwata S, Ohno M, et al. Prognosis of patients with heart failure and obstructive sleep apnea treated with continuous positive airway pressure. Chest. 2008;133(3):690-6.