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

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## 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 Sindromes / 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 men[1-3].

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 50-70[4]. 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 mortality[2,3].

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 population[1-4].

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 hypoxia[5].

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 authors[5-8], 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 ratings[2,3].

Evidence from clinical studies revealed that patients with non-treated SAS have a higher death risk comparing to patients with treatment[9]. There are several methods of treatment such as noninvasive ventilation, oral prostheses, surgical procedures, pharmacological therapies and sleep hygiene[10-14].

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.

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## 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 5.1[16].

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 $I^2$ (which indicates the proportion of variability between studies, providing a measure of heterogeneity). We considered the sample was homogeneous for a value of $p \geq 0.05$ in *Q* test and $I^2$ value of $\leq 25\%$.

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 $p \leq 0.05$ for a 95% CI. The funnel plot was used to detect eventual publication bias (Y-axis – Study weight or sample size; X-axis – 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 $I^2 = 41\%$ 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 al[24] and Sahlin et al[5] CI (Figure 2), a greater difference between CI values can be seen from this two studies comparing to estimated CI value (Masuda et al[24] – CI: 1.97 – 15.78; Sahlin et al[5] – 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

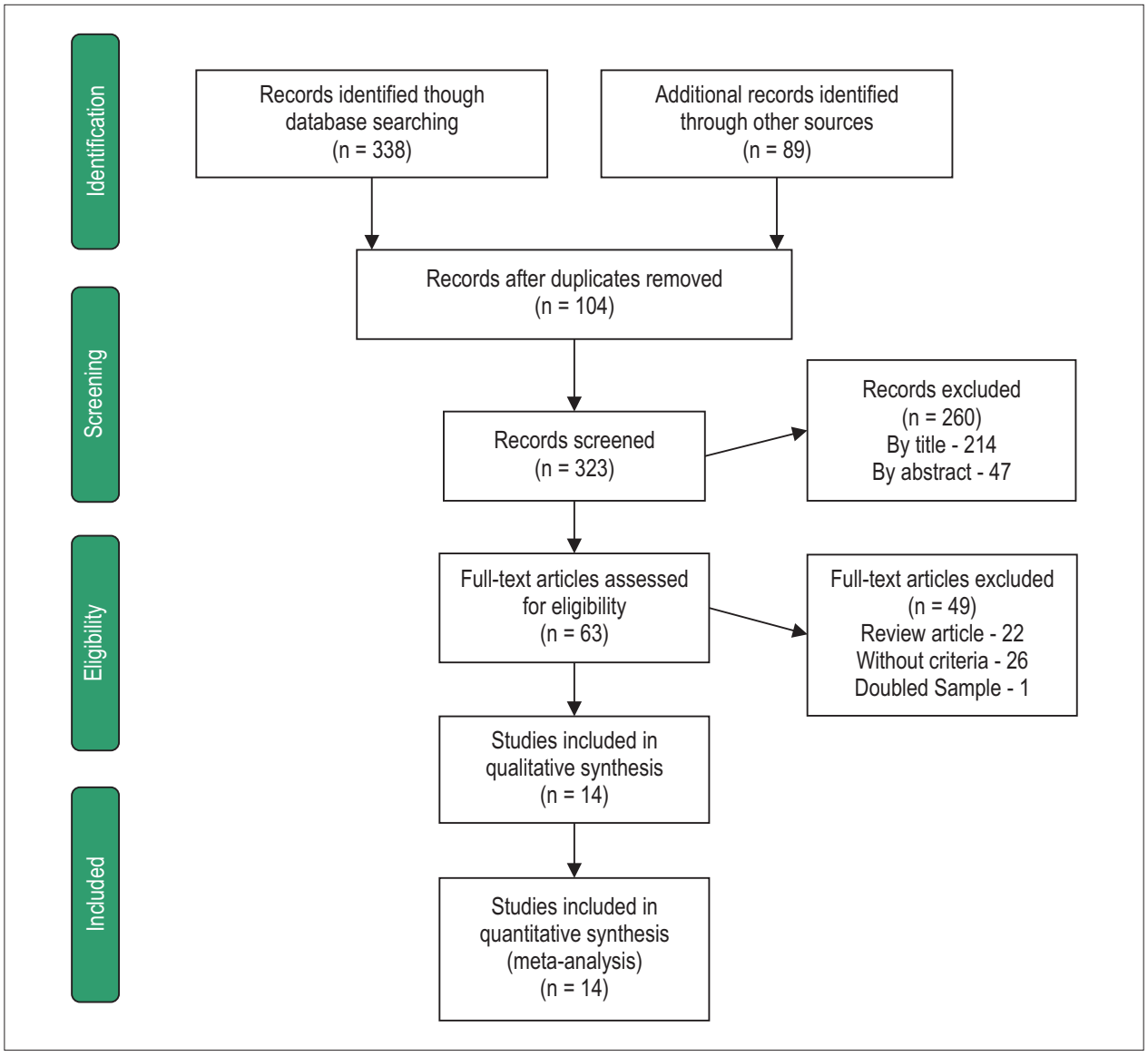


**Figure 1 –** *Process of selection of studies.*

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 | | Total |
|---|---|---|---|
| | Non-SAS | SAS | |
| 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.*

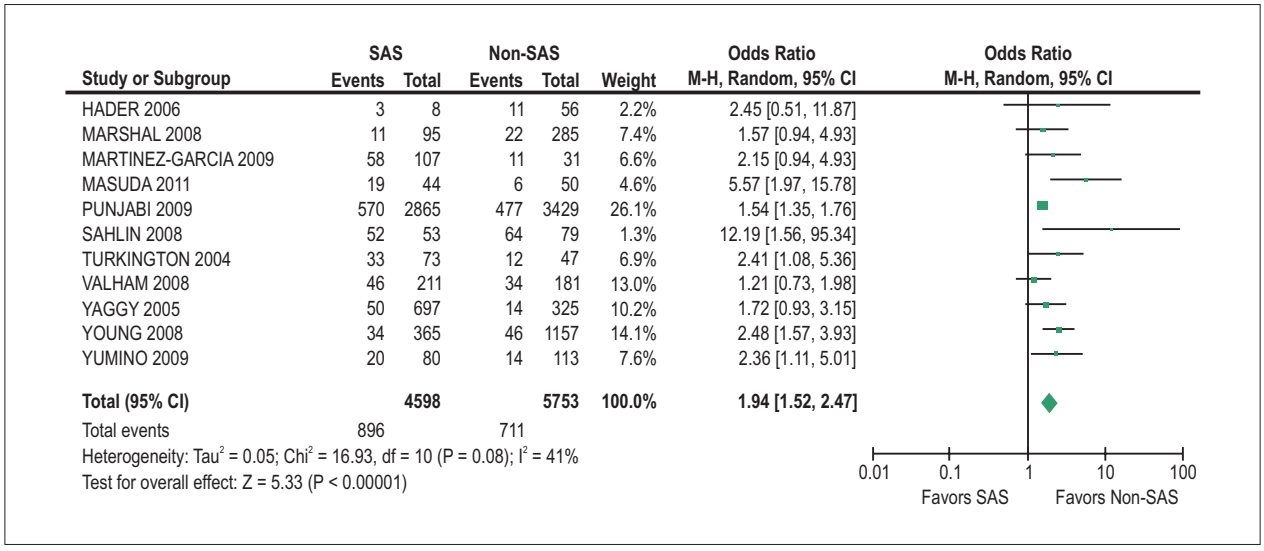


**Figure 2 –** *Mortality Outcome – Random-effects analysis (Odds Ratio)*
*Turkington et al[17]; Yaggy et al[18]; Hader et al[9]; Marshal et al[20]; Sahlin et al[5]; Young et al[2]; Valham et al[21]; Punjabi et al[8]; Martínez-García et al[22]; Yumino e cols.[23]; Masuda e cols.[24].*

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 $I^2$ = 0%, plus a symmetric distribution in the funnel plot.

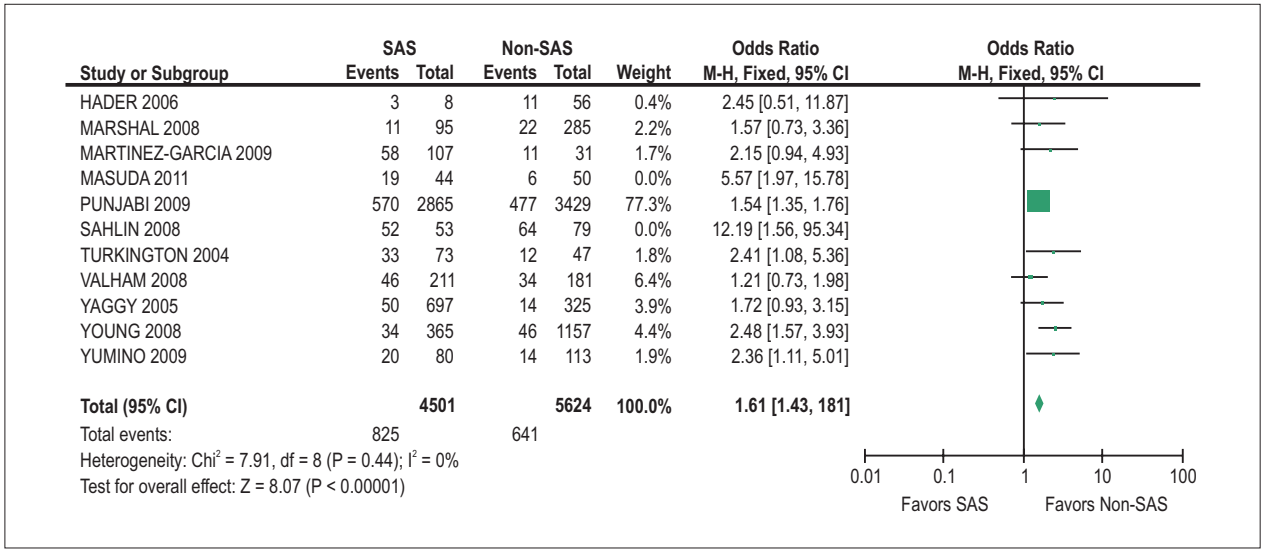


**Figure 3 –** *Sensitivity analysis – Fixed Analysis*
*Turkington et al[17]; Yaggy et al[18]; Hader et al[19]; Marshal et al[20]; Sahlin et al[5]; Young et al[2]; Valham et al[21]; Punjabi et al[9]; Martínez-García et al[22]; Yumino et al[23]; Masuda et al[24].*

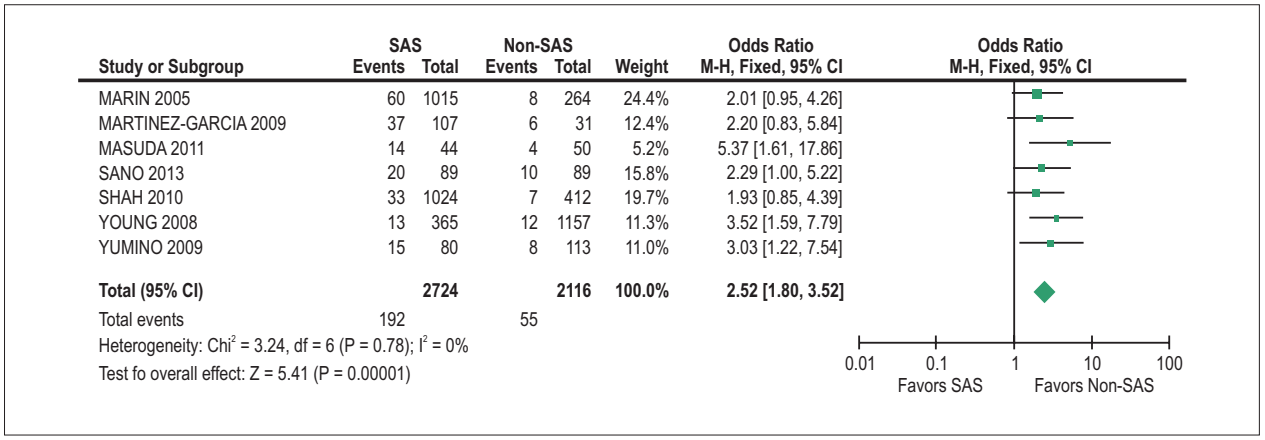


**Figure 4 –** CV death *Outcome* – Fixed Analysis (Odds Ratio)
*Marin et al[25]; Young et al[2]; Martínez-García et al[22]; Yumino et al[23]; Shah et al[26]; Masuda et al[24]; Sano et al[27].*

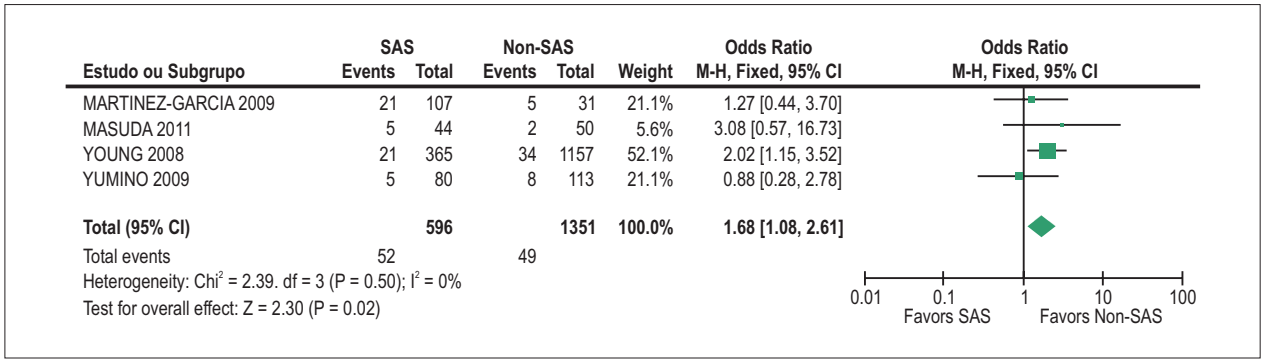


**Figure 5 –** *Death from other causes Outcome – Fixed Analysis (Odds Ratio)*
*Young et al[2]; Martínez-García et al[22]; Yumino et al[23]; Masuda et al[24].*

### 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; $I^2$ = 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 dysfunction[1,28-33]. 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 stroke[1,31]. 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 arrhythmias[32]. Furthermore, acute MI is also highly prevalent in patients with SAS, being either a cause or a consequence of SAS[19]. This may also contribute to an increased number of fatal and non-fatal events in patients with SAS.

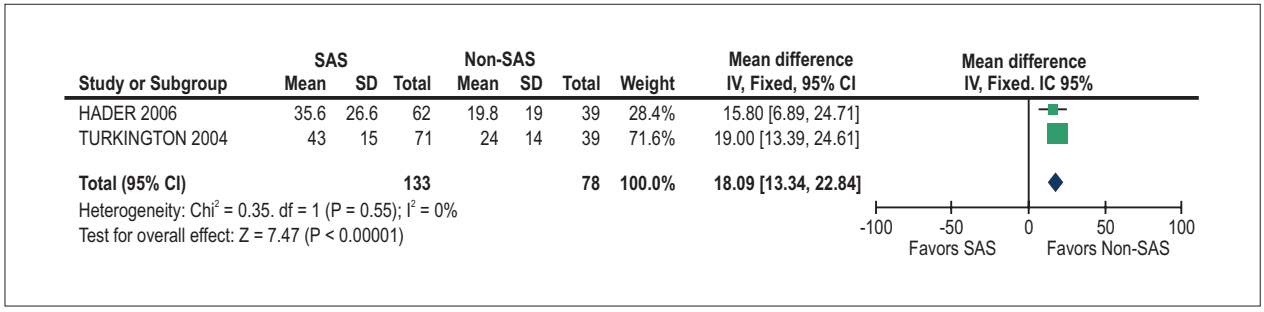


**Figure 6 –** *Mean hospitalization days Outcome – Fixed Analysis (Mean Difference) Turkington et al[17]; Hader et al[19].*

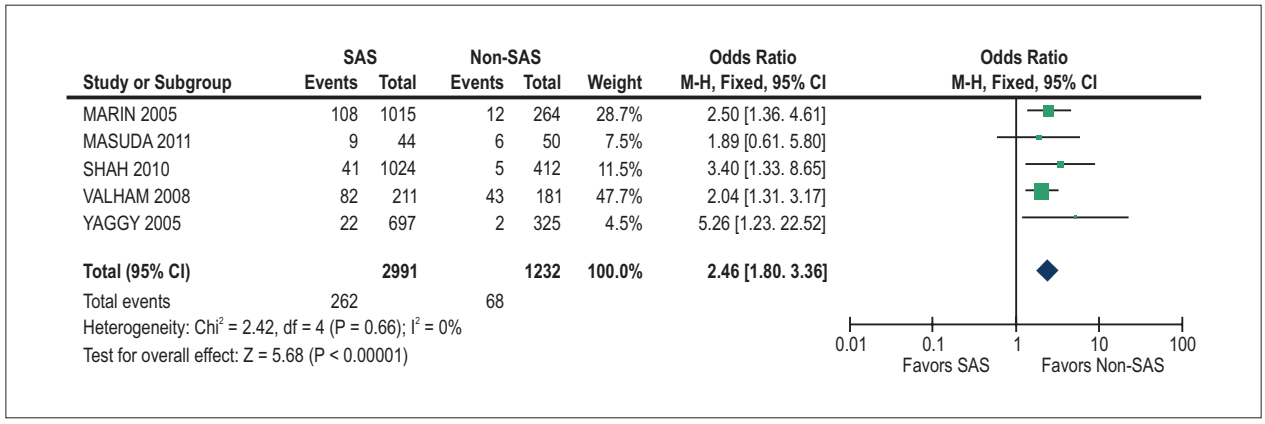


**Figure 7 –** *Non-Fatal CV events – Fixed Analysis (Odds Ratio) Marin et al[25]; Yaggy et al[18]; Valham et al[21]; Masuda et al[24].*

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[22]; Sahlin et al[5]; Valham et al[21]; Sano et al[27]; Masuda et al[24]; Yumino et al[23]; Turkington et al[17]; Hader et al[9]], other studies have evaluated patients with SAS symptoms [Marin et al[25]; Yaggy et al[18]; Shah et al[26]], 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[9].

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 e cols.[22]: AHI 0 – 9 events/hour; Sahlin e cols.[5]: AHI < 15 events/hour; Yumino e cols.[23]: AHI < 15 events/hour; Turkington e cols.[17]: RDI < 10 events/hour). This fact may have contributed to some of the heterogeneity of the results, thus motivating the adoption of random effects analyzes, in some cases, supplemented with sensitivity analyzes[5,17,22,23]. 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[18,22,33,34-39]. 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 anc 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.

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### Study Association

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