



Mortality in Obstructive Sleep Apnea

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- Mortality as an outcome
Markers of disease severity in obstructive sleep apnea
Cohort versus randomized controlled trials
- Obesity and mortality
- Mortality studies in obstructive sleep apnea before 1995
- Mortality studies in obstructive sleep apnea after 1995
- The Zaragoza sleep cohort study
- Effect of continuous positive airway pressure on mortality in obstructive sleep apnea
- Summary
- References

Obstructive sleep apnea (OSA) is a frequent disease that affects 4% of middle-age men and 2% of middle-age women [1,2]. OSA is characterized by recurrent collapse of the pharyngeal airway during sleep. In those episodes, respiratory effort is present and arterial oxygen saturation decreases, terminated by an arousal from sleep. The two main clinical consequences of OSA are daytime sleepiness and cardiovascular sequelae, which are responsible for the potential increased morbidity and mortality associated with this condition (Fig. 1). Increased traffic accidents in untreated OSA patients compared with non-OSA patients have been demonstrated [3,4], but the cardiovascular consequences of OSA are still a subject of debate [5,6]. This article examines the growing evidence that links OSA with cardiovascular outcomes and specifically with an excess of mortality.

Mortality as an outcome

The term “outcome” is designed to evaluate the consequences of the disease as experienced by the patient, death being the main outcome of any medical entity. In OSA, outcomes include daytime sleepiness; snoring; morning hangover; poor health-related quality of life; increased health resource use; cardiovascular outcomes (systemic hypertension, myocardial infarction, stroke, congestive heart disease); and death (Box 1). Some clinical outcomes, such as drowsiness or snoring, are easily measured within routine practice and in the setting of a clinical trial and are very sensitive to medical intervention [7,8]. Others, such as cardiovascular outcomes or death, are subjected to comorbid conditions that make it more difficult to establish the specific role of OSA. As a consequence,

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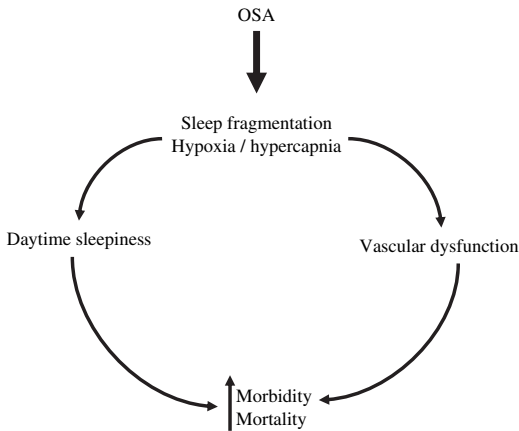


Fig. 1. Clinical consequences of obstructive sleep apnea.

in OSA, studies designed to evaluate the effects of treatment directly on cardiovascular and mortality outcomes are impracticable and unethical, because these clinical outcomes may need to run for a long time in otherwise symptomatic patients for whom an effective treatment is available [9]. Death is the strongest outcome in clinical trials. Some studies done in the cardiology field with antihypertensive drugs have shown that the active drug produced a modest reduction in blood pressure numbers and no modification in left ventricular ejection fraction [10]. Because the active drug also showed an increase in survival, however, these medications are included in the treatment guidelines of chronic heart failure.

Markers of disease severity in obstructive sleep apnea

A “marker” is a measurement known to be associated with a clinical outcome. In OSA, the best widely accepted marker of disease severity is the apnea-hypopnea index (AHI), which is the number of apneas and hypopneas per hour of sleep. The

Box 1: Hierarchy of clinical outcomes in OSA

Death
Cardiovascular

- Nonfatal myocardial infarction
- Nonfatal stroke or transient ischemic attack
- Heart failure
- Pulmonary hypertension
- Cardiac arrhythmias
- Systemic hypertension

Traffic accidents
Health quality of life
Daytime sleepiness

AHI is used not only to define the OSA syndrome (AHI >5 plus daytime sleepiness) but also serves to stratify OSA severity: mild OSA (AHI between 5 and 15); moderate OSA (AHI between 16 and 30); and severe OSA (AHI >30) [11]. Some have argued that this classification is arbitrary, because there are little data evaluating the relationship between the AHI and daytime symptom severity. Nevertheless, recent studies proved helpful in OSA severity stratification by AHI as a marker for cardiovascular morbidity and mortality in long-term cohort studies [12–14]. Oxygen desaturation, sleep disruption, and total sleep time are important pathologic processes that go together with apnea episodes. It is possible that these factors act as markers of disease severity and outcomes in OSA, but there are even less data on the literature addressing the issue. Until a gold standard marker is widely accepted, AHI could be considered the best surrogate of OSA severity as a sleep-disordered breathing.

Cohort versus randomized controlled trials

Evidence for an association of a marker and an outcome comes from different kinds of studies that can be grouped (Fig. 2). Randomized controlled trials are the most robust tools because they have fewer biases and have proved to have the best inference. Cross-sectional studies are often flawed by confounding variables, which are unknown before the study is designed, so they provide weaker and more biased inference. Most epidemiologists consider cohort observational studies as suggestive of an association between specific markers and outcomes, but with no definitive proof of that relationship. The main criticism is that in the observational studies the effects of an intervention (eg, nasal continuous positive airway pressure [CPAP] in OSA) may be caused by an unrecognized confounding factor rather than the effect of treatment. Well-conducted randomized controlled trials have the clear advantage over observational studies in that they control for both known and unknown or unmeasured confounding factors, such as life course socioeconomic position and doctor selection practices. They are not always feasible, however, and because of the expense and ethical concerns of randomized trials, it is important that observational studies be

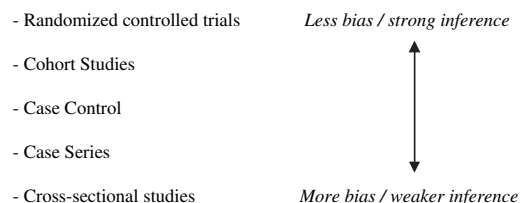


Fig. 2. Levels of evidence in clinical studies.

used effectively to direct investigators to the interventions most appropriately assessed by trials.

In OSA there are no long-term randomized controlled trials assessing the natural history of the disease and the therapy impact on robust fatal and nonfatal cardiovascular outcomes. These studies are only feasible in asymptomatic patients because the symptomatic should receive an effective treatment, such as nasal CPAP. Nevertheless, several reviews have suggested that well-planned observational studies provide information that closely resembles that provided by randomized trials [15,16].

Obesity and mortality

Most patients with OSA are overweight or obese. Obesity is associated with reduced chest wall compliance, decreased lung volumes, and increased upper airway resistance [17]. Adiposity of the neck also promotes the collapse of upper airway during sleep [18]. All of these factors contribute to increase the severity of the nocturnal respiratory events, and there is a linear relationship between body weight and the frequency of respiratory events during sleep [19]. Some authors have argued that, because obesity per se carries an increase in cardiovascular morbidity and mortality, it is likely that weight (more specifically upper body obesity) and not the AHI value is responsible for increases in such outcomes [20,21].

Recently, Adams and colleagues [22] published the results of a 10-year follow-up of a very large cohort of men and women in the United States recruited from the general population. They found an increased risk of death with excess body weight. The risk of death increases by 20% to 40% among overweight persons (body mass index [BMI] of 25–29.9 kg/m²) and by two to at least three times among obese persons (BMI >30 kg/m²). The results were adjusted for confounding variables, including level of education, race, alcohol consumption, and physical activity. Because OSA symptoms were not recorded and no sleep studies were done, the authors cannot rule out the possibility that sleep apnea accounted for the relationship between adiposity and the risk of death. Obesity is listed as a major modifiable cardiovascular risk factor [22]. Two thirds of patients who have had a myocardial infarction have a BMI greater than 25 [23]. A recent report of a systematic review and meta-analysis of cohort studies examining the association between bodyweight and mortality have provided some conflicting results [24]. Overweight was associated with a better survival and fewer cardiovascular events than normal BMI. Obesity was associated with an increased total mortality only in patients with

a history of coronary artery bypass graft, and severe obesity was associated with the highest cardiovascular mortality but not with increased total mortality. This study confirms the deleterious effect of obesity (BMI >30 kg/m²), but in some ways it contradicts the study by Adams and colleagues [22]. In the American study the follow-up was 10 years; follow-up here was limited to 3.8 years, which is insufficient to detect the full effect of being overweight on long-term outcomes because the full effect of obesity on cardiovascular mortality may begin after 15 years or more [25].

Obesity and OSA share several pathophysiologic pathways by which both entities increase the risk for developing vascular diseases. They reduce insulin sensitivity enhancing free fatty acid turnover, induce a hypercoagulable state, and promote systemic inflammation, all of which contribute to the development and progression of atherosclerosis [26]. Obesity and OSA are also favorable conditions for developing major cardiovascular risk factors, such as diabetes, dyslipidemia, and hypertension [27,28]. Interestingly, obesity researchers have largely ignored the possibility that results attributed to obesity might be caused by OSA. It is conceivable that OSA is an important part of the mechanism by which obesity leads to cardiovascular disease. If so, this is of fundamental significance because it opens an alternative strategy to address the growing epidemic of obesity.

Besides decreasing lung function, obesity increases cardiovascular risk, making it hard to assess the independent role of OSA on cardiovascular morbidity and mortality. The interrelationships between obesity and OSA are complex and possibly bidirectional, so obesity is a pivotal confounder that needs to be considered very carefully when designing clinical trials.

Mortality studies in obstructive sleep apnea before 1995

In 1997, Wright and colleagues [29] reported a systematic review of all studies published between 1966 and 1995 on the association between OSA and mortality. They argued that at that time there was a paucity of robust evidence for such a relationship. The paper led to a very positive outcome, because it stimulated new approaches and studies. Until 1995 only six articles with mortality as an outcome were published (Table 1). Two were retrospective and the results were not adjusted for BMI and had small samples [30,31]. The other four were prospective and three of them only included elderly population [32–35]. All six studies had many methodologic limitations because they failed adequately to take into account important confounding risk factors

Table 1: Mortality studies in OSA published before 1996

Author	Design	Total sample	Mean age	Mean AHI	Mean follow-up	Results
He et al [30]	Retrospective	385	52	35	NA	AI >20 has a RR of 1.5 versus AI <20
Gonzalez-Rothi et al [31]	Retrospective	126	46	39	3 y	RR 1.35 versus control (not significant)
Bliwise et al [32]	Prospective	298	69	NA	Up 12 y	RR of 2.7 for RDI >10 (not significant)
Ancoli-Israel et al [33]	Prospective	233	83	19	3.3 y	Significant association of AHI and death in women but not in men
Mant et al [34]	Prospective	163	83	NA	4 y	No relationship between RDI and survival
Lavie et al [35]	Prospective	1620	48	NA	12 y	OR of 1.012 for AI >10

Abbreviations: AHI, apnea-hypopnea index; AI, apnea index; OR, odds ratio; RDI, respiratory disturbance index; RR, risk ratio.

for cardiovascular diseases, such as obesity, smoking, dyslipemia, or hypertension. Overall, the results of those studies showed inconsistent results with limited evidence to link OSA with an excess of mortality.

Mortality studies in obstructive sleep apnea after 1995

To overcome the limitations of the uncontrolled studies discussed previously, we need well controlled and long-term longitudinal studies. Since the Wright paper was published, at least five longitudinal studies have confirmed increased cardiovascular mortality in OSA patients (Table 2) [12,13,36–38]. Two studies from Sweden compared the mortality of patients with verified coronary

artery disease (CAD) with and without OSA [36,37]. Both used Cox proportional hazards model to identify predictors of end points. In the study by Peker and colleagues [36], after a mean follow-up of 5 years of 62 patients with CAD, the respiratory disturbance index (RDI) remained an independent predictor of cardiovascular mortality (1.13; 95% confidence interval [CI], 1.05–1.21; $P < .001$). In a more powered study (408 patients with CAD), Moee and colleagues [37] demonstrated that an oxygen desaturation index of greater than 5 predicted a 70% relative increase in the composite end point of death, cerebrovascular events, and myocardial infarction. Similar results were seen in those with an AHI of greater than 10 events per hour. Recently, however, a 10-year survival report did not confirm that OSA worsened the prognosis of patients with

Table 2: Mortality studies in OSA published after 1996

Author	Design	Total sample	Mean age	Mean AHI	Mean follow-up	Death results
Peker et al [36]	Prospective	62	68	16	5 y	RR of 1.13 for RDI >10 (significant)
Moee et al [37]	Prospective	408	60	NA	5 y	RR of 1.60 for ODI >5 (significant)
Lavie et al [38]	Prospective	13,850	48	NA	4.5 y	HR of 2.2 for RDI >30 (significant)
Yaggi et al [13]	Prospective	1022	61	35	3.4 y	HR of 3.3 for AHI >36 (significant)
Marin et al [12]	Prospective	1651	50	32	10 y	OR of 2.87 for AHI >30 (significant)

Abbreviations: AHI, apnea-hypopnea index; AI, apnea index; HR, hazard ratio; OR, odds ratio; RDI, respiratory disturbance index; RR, risk ratio.

CAD [39]. The problem with the latter study is the small number of patients included ($N = 50$) and the failure to match OSA versus non-OSA groups for age, BMI, and hypertension. It seems that untreated OSA worsens the prognosis of patients with CAD, but the issue is not resolved and more powered studies need to be done in this field.

In OSA patients without pre-existing cardiovascular or cerebrovascular diseases, Yaggi and colleagues [13] reported an increased risk for death or stroke and a dose-effect relationship between OSA severity and risk. This study enrolled 1022 patients; 697 had an AHI greater than 5 and 325 had an AHI less than 5 and were considered the control group. After adjustment for age, gender, race, BMI, smoking and alcohol status, and the presence or absence of major cardiovascular risk, such as diabetes, hyperlipidemia, or hypertension, patients with OSA had an increased risk for the composite primary end point of stroke and death (hazard ratio (HR), 1.97; 95% CI, 1.12–3.48; $P = .01$). Interesting, in trend analysis, as the severity of AHI increases at baseline, there was an increase risk of the development of the composite end point ($P = .005$). Patients with severe OSA (AHI >36) had an HR of 3.30 in the composite outcome compared with the control group. This study showed that OSA is a risk for developing first time stroke but it was not apparent if the increase of death rate was caused by vascular causes because all-cause of death was included in the composite outcome. Unfortunately, use of nasal CPAP was not evaluated and the short duration of follow-up (3 years) and the small number of observed events did not allow the specific assessment of the effects of therapy.

All-cause mortality was also evaluated in a recent report from Israel. Lavie and colleagues [38] collected mortality information among a very large cohort of 14,589 men referred to the sleep clinics with suspected sleep apnea. After a median follow-up of 4.6 years, Cox proportional analysis revealed that both BMI and RDI were associated with mortality. The age and the BMI-adjusted hazard ratio for men with a RDI greater than 30 was 2.13 (95% CI, 1.36–2.34) compared with the reference group of patients with a RDI less than 10. In a second and very interesting analysis, the authors compared the relative mortality rates of OSA patients with the general male population in Israel. They found that the increase in all-cause mortality rates among moderate-to-severe RDI categories (RDI >30) was only significantly higher in men aged less than 50 years compared with their counterparts in the general population. The value of this study is the large numbers of patients included and the inclusion of age and BMI as confounders. Unfortunately, no other potential risk of mortality, clinical status at

diagnosis, or therapy was controlled. One important finding in this study is the confirmation of the effect of OSA on mortality in the young and middle aged. Previous less powered studies also have consistently reported that OSA is associated with increased risk of mortality among patients aged less than 50 years with the excessive risk declining after age 50 years [29,33,40]. It seems that the increased risk of mortality reported in OSA was found mainly in younger people and that, as stated by Lavie and colleagues [38], the diagnosis and treatment of sleep apnea should be done at the youngest possible age.

The Zaragoza sleep cohort study

Since the sleep clinic was setup in 1992 in the Hospital Miguel Servet, a tertiary teaching hospital serving a community of up 600,000 people, all patients assessed at baseline are studied under a predetermined protocol. Clinical data are recorded at each outpatient visit using the same standardized questionnaire [41]. Smoking and alcohol consumption status are recorded. The initial evaluation also includes routine blood tests and 12-lead electrocardiography. Blood pressure is measured and hypertension is defined as a systolic blood pressure at rest greater than or equal to 140 mm Hg, a diastolic blood pressure at rest greater than or equal to 90 mm Hg, or treatment with antihypertensive medication [42]. Medical records from hospital and family practitioners are obtained and cardiovascular risk factors are recorded. The diagnosis of diabetes mellitus and other prevalent chronic diseases is established according to the clinical history and use of specific medications, as revealed by the patient or chart review. A full polysomnographic study is obtained in all participants at entry. In keeping with national guidelines, nasal CPAP is recommended to all patients with an AHI greater than or equal to 30 [43]. If the AHI was between 5 and 30, CPAP was equally recommended whenever the patient complained of severe daytime sleepiness that interfered with daily activities or if there was coexistent polycythemia or cardiac failure.

In 2005, the authors reported the long-term cardiovascular outcomes in men with OSA referred to the sleep unit between January 1, 1992, and December 31, 1994 [12]. During the recruitment period 1465 patients had polysomnography and treatment with CPAP was recommended to 667 patients. Patients not treated with nasal CPAP received conservative maneuvers: weight loss; alcohol-sedative avoidance; smoking cessation; avoidance of sleep deprivation; and, if appropriate, sleep position restriction. Patients attended the clinic yearly. During these visits, compliance with CPAP therapy was

assessed by the timer built into each CPAP device. A mean daily use of more than 4 hours per day was considered necessary to maintain the CPAP prescription. During the last semester of the year 2003, all patients were contacted by telephone or letter and invited to visit the clinic for examination and to update medical information. There was also the opportunity to evaluate outcomes of healthy male subjects recruited from the Zaragoza Sleep Apnoea Prevalence Study database, a population-based study performed during 1991 and 1992 [41]. In that study, participants completed a general health and a specific sleep questionnaire, and had a polysomnographic study. For the purpose of the current investigation, men who denied excessive daytime somnolence and who did not snore ever as reported by a close relative were selected. Of 277 potential candidates, 268 subjects had an AHI less than 5 and were followed-up.

After a mean of 10.1 years, 264 healthy men, 377 simple snorers, 403 with untreated mild-moderate OSA (AHI <30), 235 with untreated severe OSA (AHI >30), and 372 with OSA treated with CPAP were included in the analysis. Patients with untreated severe OSA had a higher incidence rate of fatal events (1.06 events per 100 person-years) than untreated patients with mild-moderate OSA (0.55 events, <0.02); simple snorers (0.34 events, $P < .0005$); patients treated with nasal CPAP (0.35 events, $P < .005$); and healthy subjects (0.3 events, $P < .005$). Multivariate analysis adjusted for potential confounders showed that untreated severe OSA increased significantly the risk of fatal cardiovascular events (odds ratio 2.87; 95% CI, 1.17–7.51) compared with healthy subjects (Table 3). This was

Table 3: Fully adjusted odds ratio for cardiovascular death associated to clinical variables and diagnosis status, according to the logistic-regression analysis

	OR (95% CI)	P value
Age (y)	1.09 (1.04–1.12)	0.001
Diagnostic group		
Snoring	1.03 (0.31–1.84)	0.88
Mild-moderate OSA	1.15 (0.34–2.69)	0.71
Severe OSA	2.87 (1.17–7.51)	0.025
CPAP	1.05 (0.39–2.21)	0.74
Presence of CV disease	2.54 (1.31–4.99)	0.005

Abbreviations: CPAP, continuous positive airway pressure; CV, cardiovascular; OSA, obstructive sleep apnea. **Data from** Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046–53.

not the case in untreated patients with mild-moderate OSA, simple snorers, or patients treated with nasal CPAP. It was concluded from this large, long-term, prospective, controlled study that in untreated male patients with severe OSA, the risk of fatal cardiovascular events is increased, there is a dose-effect relationship between the severity of OSA and cardiovascular risk, and simple snoring is not a significant cardiovascular risk factor (Fig. 3). When these results are combined with the previously mentioned revised results, one sees a picture (Fig. 4), in which the risk of death among patients with severe OSA can be considered around 3 times compared with the general population or those of patients with just mild OSA.

Effect of continuous positive airway pressure on mortality in obstructive sleep apnea

Nasal CPAP can effectively treat OSA during sleep [7,8]. Acceptance of CPAP therapy remains a problem in patients without excessive daytime somnolence, however, and in this particular group of nonsleepy patients this device has no benefits [44]. Studies to date regarding the impact of CPAP in OSA used short-term outcomes (<6 months). Few longitudinal studies have assessed death as an outcome until recently. It is possible that nasal CPAP decreases the total mortality in OSA patients because it reduces car accidents [45], but no data are definitely available in the literature.

The first study on long-term survival of patients with OSA treated with CPAP was reported by He and colleagues [29]. In their series, none of the patients treated with tracheostomy or nasal CPAP died after a minimum of 5 years. The opposite was found

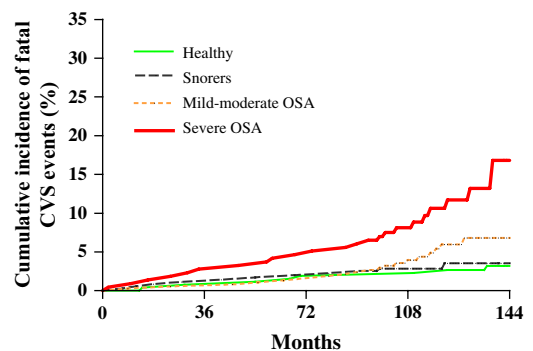


Fig. 3. Cumulative percentage of individuals with fatal cardiovascular events in non-treated with nasal CPAP groups. (Adapted from Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046–53; with permission.)

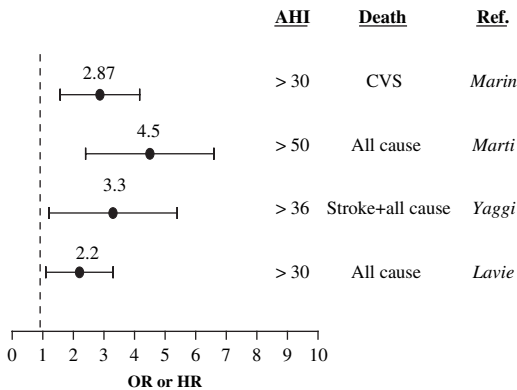


Fig. 4. Summary of the risk of death in the prospective and controlled studies addressing the issue of the relationship of OSA and mortality.

by another noncontrolled study comparing the effect of CPAP with uvulopalatopharyngoplasty; no decrease in survival was found with either therapy compared with no treatment [46]. Both studies lack methodologic precision. More recently, a study from Spain determined survival rates and causes of death in a large group of OSA patients who had been treated with CPAP for a long period of time. This study also analyzed CPAP compliance [47]. They found that mortality rates at 5 years in OSA patients who did not receive CPAP therapy were higher compared with those treated with CPAP (3.4% versus 14.5%; $P < .0001$). Also from Spain, Marti and colleagues [40] reported the long-term survival of a historical large cohort of OSA patients who had been followed-up for up to 14 years. Patients with severe OSA who accepted CPAP and were compliant with the therapy had a reduction of 40% in all-cause mortality compared with those subjects who refused the therapy. The excess cardiovascular fatal events occurred in patients aged less than 50 years who refused CPAP treatment, a finding that supports the high mortality of younger people with untreated OSA. Doherty and colleagues [48] from Ireland also performed a long-term follow-up study of 168 patients with OSA who began CPAP therapy for at least 5 years previously. Incidence of hypertension, ischemic heart disease, and other cardiovascular disorders during follow-up was not significantly different in treated and untreated patients, irrespective of acceptance or refusal of CPAP treatment. Only untreated patients showed excess cardiovascular mortality during follow-up, however, compared with those who accept CPAP (14.8% versus 1.9%).

The authors' sleep cohort study also supports the benefit of CPAP in survival among severe OSA patients [12]. After 10 years of follow-up, severe OSA patients under CPAP treatment had an adjusted

odds ratio for fatal cardiovascular mortality that did not differ significantly from non-OSA healthy individuals. The results suggest that treatment with CPAP for at least 4 hours per nights significantly reduces the raised cardiovascular risk reported in untreated severe OSA.

Summary

Many recent prospective, long-term, controlled studies suggest that in untreated patients with sleep apnea, the risk of death from all causes and particularly cardiovascular causes is increased. There is a relation between the severity of this disease and cardiovascular risk, but the effective treatment with nasal CPAP significantly reduces the mortality associated with this medical condition. Nevertheless, clinicians must go forward because of the research in the field. From a public health point this is a cost-effective investment, because CPAP treatment seems to decrease the excess health care costs for cardiovascular disease and car accidents incurred by OSA [49].

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