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# Severity of OSAS, CPAP and cardiovascular events: A follow-up study

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## Abstract

**Background:** Previous studies suggested obstructive sleep apnoea syndrome (OSAS) as a major risk factor for incident cardiovascular events. However, the relationship between OSAS severity, the use of continuous positive airway pressure (CPAP) treatment and the development of cardiovascular disease is still matter of debate.

**Study objectives:** The aim was to test the association between OSAS and cardiovascular events in patients with concomitant cardio-metabolic diseases and the potential impact of CPAP therapy on cardiovascular outcomes.

**Methods:** Prospective observational cohort study of consecutive outpatients with suspected metabolic disorders who had complete clinical and biochemical workup including polysomnography because of heavy snoring and possible OSAS. The primary endpoint was a composite of major adverse cardiovascular and cerebrovascular events (MACCE).

**Results:** Median follow-up was 81.3 months, including 434 patients (2701.2 person/years); 83 had a primary snoring, 84 had mild, 93 moderate and 174 severe OSAS, respectively. The incidence of MACCE was 0.8% per year (95% confidence interval [CI] 0.2-2.1) in primary snorers and 2.1% per year (95% CI 1.5-2.8) for those with OSAS. A positive association was observed between event-free survival and OSAS severity (log-rank test; $P = .041$). A multivariable Cox regression analysis showed obesity (HR = 8.011, 95% CI 1.071-59.922, $P = .043$), moderate OSAS (vs non-OSAS HR = 3.853, 95% CI 1.069-13.879, $P = .039$) and severe OSAS (vs non-OSAS HR = 3.540, 95% CI 1.026-12.217, $P = .045$) as predictors of MACCE. No significant association was observed between CPAP treatment and MACCE (log-rank test; $P = .227$).

**Conclusions:** Our findings support the role of moderate/severe OSAS as a risk factor for incident MACCE. CPAP treatment was not associated with a lower rate of MACCE.

**KEYWORDS**

cardiovascular disease, continuous positive air pressure, metabolic syndrome, obstructive sleep apnoea syndrome

Baratta and Pastori equally contributed to this study.

# 1 | INTRODUCTION

Obstructive sleep apnoea syndrome (OSAS) is a common sleep-related breathing disorder characterized by daytime sleepiness, the presence of repetitive apnoea and hypopnoea, and cardiopulmonary modifications. Patients with OSAS experience recurrent episodes of cessation of breathing, which expose the cardiovascular system to cycles of hypoxia, exaggerated negative intrathoracic pressure and arousals.[1-3]

The majority of patients with OSAS show a cluster of cardio-metabolic risk factors, and it has also been suggested that OSAS may be regarded to as a manifestation of metabolic syndrome.[4] OSAS is highly prevalent in patients with established cardiovascular disease, such as in subjects with hypertension, heart failure, ischaemic heart disease and stroke.[5-7] Observational cohort studies suggested OSAS as an important risk factor for stroke, heart failure and mortality, while the association with coronary heart disease is more controversial.[8,9]

Although most of prospective data suggested a significant association between OSAS and cardiovascular disease, some aspects are yet to be completely clarified, such as the impact of severity of OSAS on outcomes.

Continuous positive airway pressure treatment (CPAP) is recommended for patients with moderate/severe OSAS. CPAP was shown to improve sleepiness and ameliorates quality of life and mood in the more severe and symptomatic patients. Increasing data support that effective (at least 4 hours per night) long-term treatment of severe OSAS by CPAP could be also a useful treatment for the prevention of fatal and nonfatal cardiovascular (CVD) events.[10-14] By contrast, the prescription of CPAP treatment did not appear to reduce long-term CVD events in patients with minimally symptomatic OSAS[15,16] and in those with established cardiovascular disease.[17] Moreover, two recent meta-analyses showed that CPAP use, compared with usual care, was not associated with improved cardiovascular outcomes and death in patients with OSAS.[18,19] Despite this evidence, in specific subgroups of patients with OSAS, such as those with severe disease, the use of CPAP for at least 4 hours during night-time was shown to be associated with improved cardiovascular outcomes.[10]

The aim of this study was to test the association between OSAS severity and major cardiovascular and cerebrovascular events (MACCE) in a long-term follow-up, and to investigate the potential impact of CPAP therapy on cardiovascular outcomes.

# 2 | MATERIALS AND METHODS

Patients with heavy snoring and possible OSAS who were consecutively referred to the Day Service for the treatment of metabolic diseases of Umberto I University Hospital of Rome were included. They had a complete clinical and biochemical workup including polysomnography (see below). Written consent was obtained from all subjects before the study, and the study conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The research protocol was approved by the Department of Experimental Medicine and Pathology of Sapienza University of Rome Scientific Board.

Exclusion criteria for the study were the presence of heart failure, autoimmune disease, acute inflammatory disease and any severe disease shortening life expectancy, such as cancer, chronic liver disease, severe renal disease.

Waist circumference, height and weight were recorded with subjects wearing light clothing without shoes, and body mass index (BMI) was calculated as weight (Kg) divided by height ($m^2$). Arterial blood pressure was measured on the right arm with the subjects in a sitting position and after a 5-minute rest, using a mercury sphygmomanometer: the average of two measurements, 1 minute apart, was considered. Metabolic syndrome was diagnosed according to the modified criteria of the ATP III Expert Panel of the US-NCEP.[20] Diabetes was diagnosed according to the WHO criteria. Subjects taking insulin or oral antidiabetic drugs were considered as having diabetes.

## 2.1 | Blood sampling protocol

Fasting venous blood samples were taken in the supine position on the morning after performing polysomnography and stored at −80°C until assay. Subjects underwent routine biochemical evaluation including fasting total and HDL cholesterol, triglycerides, glucose and insulin. Serum total cholesterol, HDL cholesterol and triglycerides were measured by an Olympus AN 560 apparatus using an enzymatic colorimetric method. LDL cholesterol levels were calculated according to the Friedewald formula. Plasma insulin levels were assayed by commercially available radioimmunoassay.

## 2.2 | Polysomnography (nocturnal recording)

Patients underwent unattended overnight home polysomnography (PSG) using an overnight home sleep recording (Embletta, PDS; Medcare, Reykjavik, Iceland). The device recorded nasal and oral airflow, chest and abdominal movements, and pulse oximetry; no electroencephalography trace was recorded. The sleep recordings were downloaded to a computer and scored by a principal investigator. A minimum of 4 hours of recording was accepted to be adequate for scoring. The presence and severity of apnoea were assessed based on the number of apnoea/hypopnoea episodes per hour of sleep (apnoea/hypopnoea index, AHI). Apnoea was defined as continuous

cessation of airflow for more than 10 seconds, and hypopnoea was defined as reduction in airflow for more than 10 seconds with oxygen desaturation of ≥4% and arousal. The presence of OSAS was defined as an AHI of ≥5. In particular, patients were categorized into four groups according to OSAS severity: (i) snorers without OSAS with AHI <5 events/h; (ii) mild OSAS with AHI ≥5 and <15 events/h; (iii) moderate OSAS with AHI ≥15 and <30 events/h; and (iv) severe OSAS with AHI ≥30 events/h.[21]

Each subject had overnight home pulse oximetry monitoring with a transcutaneous fingertip sensor connected via cable to an Ohmeda Biox 3700 pulse oximeter (Louisville, CO). The mean haemoglobin oxygen saturation level ($SaO_2$) in total sleep time was also calculated.

Patients with moderate/severe OSAS and those with severe daytime sleepiness (defined as sleepiness severely impairing normal daily activity) underwent a full-night nCPAP titration study at home using an automated pressure setting device. Adherence to nCPAP was defined as nCPAP use for at least 4 hours per night and 5 d/wk.

## 2.3 | Follow-up

Participants were followed from their first PSG to the end of 2016 or the occurrence of a primary endpoint, whichever occurred first. Subjects had periodical follow-up visits including clinical and biochemical evaluation and assessment of adherence to CPAP. All patients received periodical assessment of major cardiovascular risk factors and the best available medical care especially for the treatment of metabolic comorbidities. During the first quarter of 2017, all patients were contacted by telephone and asked to attend an end of study follow-up visit in the clinic. Mortality status and time of death were recorded. Multiple concurrent approaches were used to collect clinical data, including written questionnaires, follow-up interviews or telephone contacts with participants or next of kin. Further, clinical information was obtained from medical records of patients and patients' relatives. An independent board reviewed data from clinical records and death certificates. Information on prevalent cardiovascular disease was defined as history of physician-diagnosed heart failure, angina, myocardial infarction, stroke and coronary revascularization.

## 2.4 | Study endpoints

The primary endpoint was a composite of MACCE including fatal/nonfatal myocardial infarction (MI),[22] unstable angina,[23] coronary revascularization procedures (coronary artery bypass graft and/or percutaneous transluminal coronary angioplasty), fatal/nonfatal ischaemic stroke,[24] transient ischaemic attack (TIA),[25] hospitalization for heart failure and cardiovascular death (defined as sudden death, and death not related to any other evident cause of death).

## 2.5 | Statistical analysis

Continuous variables were reported as mean ± standard deviation or median with interquartile range (IQR) depending on their distribution. Student's $t$ test or Mann-Whitney test was used to compare means and medians, respectively. Group comparisons were performed by ANOVA or Kruskal-Wallis test, when appropriate. Dichotomous variables were reported as numbers and percentages. Differences were tested using the $\chi^2$ test for categorical variables. Pearson's $r$ coefficients were calculated for bivariate correlations. The cumulative incidence of MACCE according to the above-mentioned OSAS categories was estimated using a Kaplan-Meier product-limit estimator. Survival curves were then formally compared using the log-rank test. Multivariable Cox regression analysis was used to calculate the adjusted relative hazard ratios (HR) by each clinical variable after controlling for age, female sex, previous MI/stroke, OSAS categories, hypertension, diabetes, obesity (ie high waist circumference). As a secondary endpoint, we analysed the incidence of MACCE according to the use or nonuse of CPAP controlling for the same factors mentioned before. All analyses were performed using SPSS V.18.0 (Armonk, USA). All tests were two-tailed, and only $P$ values <.05 were considered as statistically significant.

## 2.6 | Power calculation

Based on previous data, a minimal sample size of 60 patients with severe OSAS and 60 controls was planned, to have a power of 80%, with significance level set to 5%, to reject a log-rank test, calculating an expected survival probability at the end of the study period (6 years) of 3% for the control group and 20% in the group of patients with severe OSAS.

# 3 | RESULTS

## 3.1 | Baseline characteristics

At baseline, diagnostic sleep study and complete clinical workup were performed in 483 subjects. However, 49 of these were lost at follow-up or had incomplete data. Excluded subjects had similar OSAS severity and demographic and clinical characteristics. Therefore, for the follow-up study, the final cohort included 434 individuals with complete baseline data; 81 had a primary snoring, 80 had mild, 96 had moderate and 177 had severe OSAS, respectively.

Baseline characteristics of the study population by OSAS severity are reported in Table 1. A positive association was observed between OSAS severity, male gender and the indices of central obesity, that is body mass index and waist circumference. In addition, a significantly higher prevalence of the metabolic syndrome was observed in subjects with severe OSAS compared to primary snorers (Table 1) AHI was strongly correlated with the number of components of the metabolic syndrome ($r = .12$; $P = .01$) and with the indices of central obesity (BMI: $r = .17$; $P = .001$ and waist circumference: $r = .289$; $P < .001$).

Fifty subjects at baseline were found to have had a previous MI or cardiac revascularization (n = 43) and/or a stroke/TIA (n = 11). Prevalence of previous cardiovascular events was similar in OSAS participants and in those with no sleep-disordered breathing. In subjects with OSAS, 46 (13.1%) had a previous CV event: 21 had MI, 7 cardiac revascularizations, 9 ischaemic strokes and 9 TIA. Three subjects with primary snoring had a previous MI and one a previous stroke.

## 3.2 | MACCE and OSAS severity

The median follow-up was 81.3 (IQR 30.5/108.9) months yielding 2701.2 person/years of observation. During the study period, 50 patients experienced the primary composite endpoint and 6 had noncardiovascular death. MACCE were 24 MI, 10 ischaemic strokes, 9 TIA, 7 coronary revascularizations, 8 cardiovascular deaths. The incidence of MACCE was 0.8 (95% CI 0.2-2.1) per 100 person/years in primary snorers and 2.1 (95% CI 1.5-2.8) per 100 person/years for those with OSAS. Kaplan-Meier survival curves across categories of AHI (<5; ≥5 and <15; ≥15 and <30; ≥30) are reported in Figure 1, panels A-D. A

**TABLE 1** Clinical and polysomnographic characteristics of the study population

| | Snorers (AHI <5, n = 81) | Mild OSAS (AHI ≥5 < 15, n = 80) | Moderate OSAS (AHI ≥15 < 30, n = 96) | Severe OSAS (AHI ≥30, n = 177) | *P* |
|---|---|---|---|---|---|
| Age (y) | 54.8 ± 10.6 | 54.8 ± 11.6 | 58.6 ± 9.4 | 55.6 ± 11.3 | .060 |
| Women (%) | 42.0 | 35.0 | 25.0 | 15.3 | .000 |
| Body mass index (kg/m$^2$) | 30.2 ± 5.2 | 31.2 ± 4.7 | 33.4 ± 10.2 | 33.7 ± 5.3 | .000 |
| Waist circumference (cm) | 105.0 ± 13.3 | 107.5 ± 11.6 | 111.5 ± 14.0 | 116.1 ± 12.6 | .000 |
| High Waist circumference (cm) | 75.5 | 78.7 | 80.8 | 90.2 | .014 |
| Systolic blood pressure (mm Hg) | 130 (120/140) | 130 (120.0/140.0) | 135 (125.0/150.0) | 135.0 (123.5/145.0) | .019 |
| Diastolic blood pressure (mm Hg) | 80 (71/90) | 80.0 (80.0/87.0) | 82.0 (77.0/90.0) | 80.0 (80.0/90.0) | .091 |
| Total cholesterol (mmol/L) | 204.3 ± 40.9 | 200.2 ± 41.3 | 198.4 ± 40.2 | 201.2 ± 44.4 | .830 |
| HDL cholesterol (mmol/L) | 47.0 ± 11.2 | 46.1 ± 11.6 | 47.1 ± 12.9 | 42.9 ± 9.6 | .007 |
| LDL cholesterol (mmol/L) | 128.4 ± 36.4 | 121.8 ± 41.7 | 123.2 ± 34.4 | 124.6 ± 39.6 | .730 |
| Triglycerides (mg/dL) | 132. (99.0/179.2) | 136.5 (100.2/226.0) | 122.0 (87.2/193.0) | 142.0 (107.0/195.5) | .359 |
| Blood glucose (mmol/L) | 107.4 ± 25.3 | 108.9 ± 38.8 | 101.3 ± 28.0 | 106.8 ± 26.0 | .322 |
| Hypertension (%) | 51.9 | 61.8 | 69.9 | 72.0 | .030 |
| Diabetes (%) | 27.2 | 23.1 | 14.6 | 22.8 | .216 |
| Metabolic syndrome (%) | 57.5 | 55.8 | 59.1 | 68.3 | .170 |
| Smoking (%) | 26.0 | 21.1 | 19.0 | 21.1 | .274 |
| Average $SaO_2$ | 95.0 ± 1.7 | 94.2 ± 2.2 | 93.4 ± 2.1 | 90.6 ± 6.6 | .000 |
| ODI (events/h) | 6.2 ± 7.1 | 11.3 ± 9.6 | 21.1 ± 11.8 | 47.9 ± 21.3 | .000 |
| Hypertension (%) | 61.5 | 68.8 | 80.5 | 69.8 | .064 |
| Statin use (%) | 37.2 | 42.9 | 41.4 | 43.8 | .801 |
| Antihypertensive drug use (%) | 57.5 | 64.8 | 76.3 | 68.0 | .054 |
| Antiplatelet drug use (%) | 14.5 | 28.4 | 26.8 | 28.2 | .110 |
| Hypoglycaemic drug use (%) | 25.3 | 25.0 | 27.8 | 26.6 | .970 |
| CPAP (%) | / | 6.3 | 22.9 | 49.7 | .000 |
| Previous MACCE (%) | 7.4 | 10.0 | 12.5 | 10.2 | .740 |
| MACCE (rate/y) (%) | 0.8 | 1.3 | 2.3 | 2.4 | / |

AHI, apnoea/hypopnoea index; CPAP, continuous positive airway pressure; MACCE, major adverse cardiovascular and cerebrovascular events; ODI, oxygen desaturation index; $SaO_2$, oxygen saturation.

significant lower event-free survival was observed only in severe OSAS when compared to healthy snorers (log-rank test; $P = .032$) (Figure 1, panel D). Univariate Cox analysis of predictors of MACCE is reported in Table 2.

A multivariable Cox proportional hazards regression model (Table 3) showed that obesity (HR = 8.011, 95% CI 1.071-59.922, $P = .043$), moderate OSAS (vs non-OSAS HR = 3.853, 95% CI 1.069-13.879, $P = .039$) and severe OSAS (vs non-OSAS HR = 3.540, 95% CI 1.026-12.217, $P = .045$) were significantly associated with MACCE. A trend for age and diabetes was also found (Table 3).

### 3.3 | MACCE and CPAP treatment

At baseline, treatment with CPAP was proposed to patients with moderate/severe OSAS, according to PSG results. A full information on the benefit of CPAP was given, and shared decision with the patients was reached. Thus, 115 started a treatment with CPAP. Univariate Cox regression analysis showed that CPAP treatment was not associated with MACCE (HR: 1.435 (0.796-2.588), $P = .230$).

No significant association was observed between CPAP treatment and cumulative event-free survival (log-rank test; $P = .227$).

In multivariable Cox regression analysis, metabolic syndrome (HR = 2.318, 95% CI 1.066-5.042; $P = .034$) and female sex (HR = 2.158, 95% CI 1.105-4.214, $P = .024$), but not CPAP (HR = 1.579, 95% CI 0.810-3.080, $P = .180$), were statistically associated with MACCE. When we considered only patients with severe OSAS, no effect for CPAP use against MACCE was found (not shown).

## 4 | DISCUSSION

In this large prospective study performed in real-world patients with sleep-disordered breathing, we found a significant association between the incidence of MACCE and the severity of OSAS. The association was independent from age, gender, metabolic syndrome and previous cardiovascular events. These findings further support the role of OSAS as a risk factor for incident cardiovascular events. The treatment with CPAP was not associated with a lower rate of MACE in our population, even in patients with more severe OSAS.

Several longitudinal studies so far have evaluated all-cause mortality in patients with OSAS and few fatal and nonfatal CVD events. Our results are in keeping with an observational study performed in Spain where severe OSAS was associated with increased risk of fatal and nonfatal CVD events[10] and with the Wisconsin Sleep Cohort Study, including 1522 subjects with a follow-up of 13.8 years, where participants with severe OSAS at baseline had a statistically significant fivefold greater risk of CVD mortality.[26] Similar findings were obtained in a prospective cohort study in the United States, where OSAS was associated with all-cause mortality and cardiovascular disease-related mortality especially in men aged 40-70 with severe disease.[27] By contrast, in a further study of OSAS, where participants experienced a composite cardiovascular incidence of 2 per 100 person/year, other than disease severity (AHI), other OSAS-related factors, such as time spent with $SaO_2$ <90%, the number of awakening and the presence of excessive daytime sleepiness were shown as important predictors of composite CVD outcome.[28]

OSAS may promote cardiovascular disease by many different mechanisms such as negative intrathoracic pressure, haemodynamic mechanisms, increased blood pressure, chronic inflammation, platelet activation, increased ROS production and endothelial dysfunction.[29-32] These adverse events, combined with increased sympathetic vasoconstrictor activity, could also predispose to hypertension and atherosclerosis.

An important finding of our study is that CPAP treatment, compared to usual care, did not result in a statistically significant improvement of the cumulative event-free survival. We also found that the metabolic syndrome was the only independent predictor of CVD events in patients with OSAS.

No large prospective observational cohort studies so far have assessed the protective role of CPAP on CVD events in patients with OSAS. Two randomized controlled trials[16,33] have shown no benefit of CPAP treatment on CVD outcomes although in the CPAP group an improved health-related quality of life and mood were observed. In accordance, a meta-analysis of 18 randomized clinical trials reported no improvement in cardiac outcomes by use of CPAP although a significantly lower Epworth sleepiness score and a significantly lower 24-hour blood pressure in the CPAP groups were found in OSAS as compared to medical therapy alone.[19] By contrast, a longer survival and a reduced CVD risk were reported in women and in very elderly patients by further prospective cohort studies.[11,13,14] Recently, CPAP therapy improved endothelial dysfunction and decreased the levels of oxidative stress and inflammatory cytokines in patients with the metabolic syndrome.[34]

There are several strengths and limitations of this study that merit to be discussed. Strength of our study is that in contrast to many previous studies performed in otherwise healthy OSAS, we included in the follow-up study patients with concomitant chronic diseases such as abdominal obesity, metabolic syndrome, arterial hypertension, type 2 diabetes, that is a representative sample of the real-world OSAS population. Indeed, prevalence of metabolic syndrome in our severe OSAS was 70%, and 67% had hypertension. By contrast, most published papers refer to cohorts

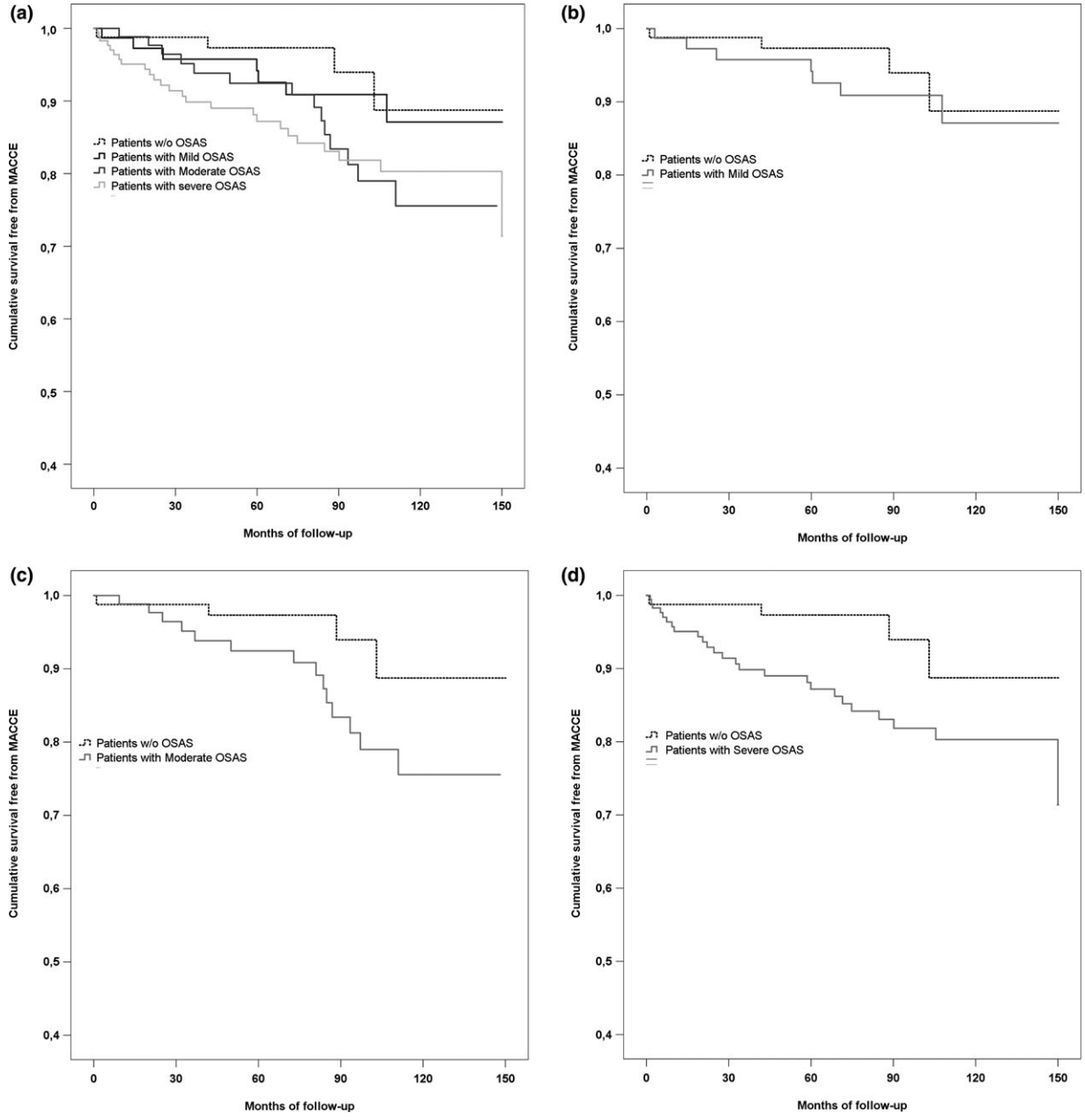


**FIGURE 1** Kaplan-Meier estimates of cumulative event-free survival probability according to obstructive sleep apnoea syndrome (OSAS) severity as expressed by the apnoea/hypopnoea index (<5; ≥5 and <15; ≥15 and <30; ≥30) (panel A); Kaplan-Meier survival curves in subjects without OSAS and those with mild OSAS (panel B), moderate OSAS (panel C) and severe OSAS (panel D), respectively

of otherwise healthy OSAS, without cardiovascular comorbidity, poorly representative of the habitual overall OSAS population.

Unattended home polysomnography should be considered as a major limitation of this study, although an excellent correlation between the results of attended polysomnography and home monitoring has been demonstrated.[35] Indeed, polysomnography and home sleep tests use the same respiratory equipment, pulse oximetry equipment, and movement and position sensors, and data generated from each test are analysed in the same manner. Home monitoring has also the ability to record in a natural sleep environment, and patients are tested in the comfort and privacy of their home. In addition, full-night nCPAP titration study at home with an automated pressure setting device rather than a conventional titration can also have resulted in nonoptimal treatment in some individuals. Another possible limiting factor could be that compliance to CPAP was evaluated only subjectively, and participants were asked to answer a questionnaire regarding their CPAP use. In fact, no objective evaluation was obtained as few CPAP devices used were equipped with automated hour

**TABLE 2** Univariate Cox proportional hazards regression analysis with variables associated with MACCE occurrence

| | HR (95% CI) | *P* value |
|---|---|---|
| Age | **1.038 (1.011-1.066)** | **.006** |
| Female Sex | 1.321 (0.727-2.402) | .361 |
| Hypertension | 1.417 (0.720-2.788) | .312 |
| High waist circumference | **10.810 (1.490-78.408)** | **.019** |
| IFG/Diabetes | 1.641 (0.961-2.940) | .096 |
| Metabolic Syndrome | **2.346 (1.164-4.729)** | **.017** |
| Smoking | 1.663 (0.844-3.275) | .141 |
| OSAS (yes/no) | 2.565 (0.922-7.139) | .071 |
| Mild OSAS (vs non-OSAS) | 1.541 (0.450-5.275) | .491 |
| Moderate OSAS (vs non-OSAS) | 2.808 (0.923-8.542) | .069 |
| Severe OSAS (vs non-OSAS) | **2.972 (1.031-8.562)** | **.044** |
| Previous MI/Stroke | 1.351 (0.534-3.420) | .526 |

IFG, impaired fasting glucose; OSAS, obstructive sleep apnoea syndrome; MACCE, major adverse cardiovascular and cerebrovascular events. Independent predictors were reported in bold.

**TABLE 3** Multivariable Cox proportional hazards regression analysis with variables associated with cardiovascular events

| | | | 95.0% Confidence interval | |
|---|---|---|---|---|
| | *P* value | Hazard ratio | Lower | Upper |
| Age | .054 | 1.030 | 1.000 | 1.061 |
| Female sex | .142 | 1.630 | 0.848 | 3.130 |
| Mild OSAS (vs non-OSAS) | .260 | 2.189 | 0.561 | 8.547 |
| Moderate OSAS (vs non-OSAS) | **.039** | **3.853** | **1.069** | **13.879** |
| Severe OSAS (vs non-OSAS) | **.045** | **3.540** | **1.026** | **12.217** |
| Hypertension | .519 | 0.779 | 0.364 | 1.665 |
| Obesity (high waist circumference) | **.043** | **8.011** | **1.071** | **59.922** |
| Previous MI/stroke | .793 | 1.138 | 0.433 | 2.989 |
| Diabetes | .081 | 1.790 | 0.930 | 3.442 |

OSAS, obstructive sleep apnoea syndrome. Independent predictors were reported in bold.

usage counters. Further limitation of the study is that no hypothesis testing on noncardiovascular outcomes can be performed because cause-specific events were only determined for cardiovascular disease. Moreover, we cannot exclude that the lack of association between CPAP and MACCE may be due to the relatively low number of patients who consented for the use of CPAP. Finally, we should acknowledge that it is difficult to demonstrate a positive effect of a single add-on treatment (here CPAP) in very well treated patients for cardiovascular prevention.

In conclusion, in our study we demonstrated a strong positive association between severity of OSAS and cardiovascular events, independent from traditional risk factors. In addition, no favourable effect of CPAP treatment on cardiovascular outcomes was demonstrated.

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## DECLARATIONS

All the authors have seen and approved the manuscript. All the authors did not receive financial support and have no conflict of interest in relation to the manuscript.

## AUTHOR CONTRIBUTIONS

Francesco Angelico is the guarantor of the manuscript. Francesco Angelico, Maria Del Ben and Mario Fabiani contributed to the study concept and design, interpretation of data, drafting of the manuscript and critical revision of the manuscript. Francesco Baratta and Daniele Pastori contributed to the study concept and design, analysis and interpretation of data, statistical analysis, drafting of the manuscript and critical revision of the manuscript. Valerio Fabiani, Marco Brunori and Gaetano Pannitteri: involved in the acquisition of data (administration of dietary questionnaire), interpretation of data, drafting of the manuscript and critical revision of the manuscript. Fabrizio Ceci, Rossella Lillo, Valeria Lolli and Elena Cravotto: involved in the acquisition of data, drafting of the manuscript and critical revision of the manuscript. Corrado De Vito: performed data analysis and interpretation. All authors read and approved the final version of the manuscript.

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