

## Determination of the Incidence of Cardiovascular Composite Events in Patients with Obstructive Sleep Apnea: A 3-year follow-up Study

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### Original Article

#### Abstract

**BACKGROUND:** The occurrence of obstructive sleep apnea (OSA) and its health-related issues, especially cardiovascular diseases (CVD), are increasing in developing countries. With a 3-year follow-up study, the present study aimed to determine the incidence of cardiovascular events in patients with OSA in an Iranian population.

**METHOD:** In this prospective cohort study, 415 adults (300 patients with OSA and 115 patients without OSA) with a history of snoring and/or witnessed apneas or other suspected sleep breathing disorders were consecutively enrolled and followed up for three successive years to evaluate the development of cardiovascular events including acute coronary syndrome, cerebrovascular accidents (including ischemic or hemorrhagic strokes or transient ischemic attacks), death due to cardiac causes and all-cause mortality.

**RESULTS:** 415 patients were studied with a mean age of  $56.2 \pm 15.7$  years, 211 (50.8) of whom were male. Cardiovascular events developed in 15 participants (5%) of the OSA group, and 3 participants (2.6 %) of the OSA negative group. No significant differences were observed between the two groups in terms of the incidence of any of these events ( $P > 0.05$ ). Using multiple logistic regression model (with  $P < 0.2$  as the significance level), age, OSA, and history of CVD remained as significant predictors for the development of cardiac composite events (incidence of CVD, CVA, death due to cardiac causes, and all-cause mortality) with the odds ratios of (95% confidence interval) 1.03 (1.01, 1.06), 2.41 (1.02, 5.76), and 7.40 (2.91, 18.67), respectively.

**CONCLUSIONS:** The present study showed that OSA is associated with a more than twofold increased risk of cardiovascular events. Thus, obstructive sleep apnea should be considered an independent cardiovascular risk factor.

**Keywords:** Sleep apnea; Cardiovascular composite events; Cerebrovascular diseases; Risk factors

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## Introduction

Obstructive sleep apnea (OSA) affects approximately 4% of men and 2% of women in the middle ages but many of these patients are not diagnosed or treated<sup>1</sup>. Obstructive sleep apnea (OSA) is defined as recurrent episodes of upper airway obstruction during sleep causing sleep arousal which leads to sleep disturbances<sup>1</sup>. OSA prevalence is increasing in developing countries, possibly due to the increasing prevalence of obesity<sup>2</sup>. OSA leads to various clinical conditions and consequences, affecting different organs<sup>3</sup>. Daytime sleepiness and sleep disturbances would impair the quality of life<sup>4</sup> and increase the risk of vehicle crashes<sup>4,5</sup>. In addition, OSA is associated with cognitive disorders and depression<sup>4-7</sup>. Cardiovascular diseases (CVD) are among the most important consequences of OSA<sup>8</sup>. A large number of studies have proved OSA as an independent risk factor of cardiovascular morbidity and mortality<sup>9</sup>. Sleep apnea was shown to be associated with hypertension, ischemic heart disease, stroke, pulmonary hypertension, cardiac arrhythmia, and cardiovascular mortality<sup>10,11</sup>. The association between OSA and hypertension has been widely studied and OSA has been established as an independent risk factor for hypertension<sup>12-14</sup>. Adults with OSA have an increased risk of developing comorbid CVD with poor CVD outcomes<sup>9</sup>. Despite widely available retrospective and cross-sectional studies, there are few prospective cohorts to demonstrate the causal link between OSA and CVD. A 3-year follow-up study was conducted on participants with and without OSA to determine the risk of cardiovascular events in patients with OSA in an Iranian population.

## Materials and Methods

### *Study population*

The present prospective cohort study was conducted on 415 adult participants. The patients included were adults aged above 18 years with a history of snoring and/or witnessed apneas or other suspected sleep breathing disorders and the patients with

OHS and individuals with a prior diagnosis of OSA were excluded. Moreover, patients with a history of Obesity Hypoventilation Syndrome (OHS) were excluded from the study. Overnight sleep evaluation was positive for OSA in 300 patients and negative in 115 patients, but participants were similar in terms of comorbidities and other socio-demographics. The overnight sleep study was initiated in the evening including AHI, Oximetry, and vital signs evaluation during night sleep. Patients were enrolled independently of a history of associated excessive daytime sleepiness. All sleep evaluations were conducted under the supervision of a board-certified sleep specialist. During polysomnography, the apnea-hypopnea index (AHI) was calculated as the sum of apnea and hypopnea episodes per hour of sleep, and OSA was defined as AHI equal to or more than 5 according to the American Academy of Sleep Medicine criteria. Questionnaires were completed for each person including age, smoking status, and metabolic risk factors such as diabetes mellitus (DM), hypertension (HTN), dyslipidemia, metabolic syndrome, and body mass index (BMI) at the baseline. History of CVD and cerebrovascular accidents (CVA) were also recruited via questionnaire. History of CVD was included using documented notes regarding myocardial infarction or even evidence of coronary artery diseases using echocardiography or other imaging modalities. All CVD events were evaluated by the scientific event committee. According to polysomnography reports, participants whose test revealed negative for OSA were categorized into OSA negative group and treated routinely under the supervision of their physician and received periodic follow-ups. Participants with positive test results for OSA were referred to a sleep specialist and treated based on the latest guideline. The baseline survey started in 2014, and follow-up of the participants was carried out every 6 months by telephone, for three years. The study protocol was approved by the Ethical Committee of Isfahan University of Medical Sciences and all participants signed informed written consent.

### *Follow-up and outcome measurement*

Gathering follow-up data and confirmation of the primary outcomes were performed blinded to the collection of baseline and polysomnographic data. Follow-up data of positive events were obtained from each subject every six months for three years after polysomnography by phone calls. Hospital documents were recruited and evaluated in the event committee consisting of two cardiologists and a pulmonologist. Cardiac events included cardiovascular diseases, Acute Coronary Syndrome (including ST-elevation and non-ST elevation myocardial infarction), cerebrovascular accident (ischemic or hemorrhagic strokes or transient ischemic attack), death due to cardiac causes, and all-cause mortality. The definition of each event was based on the International Classification of Disease (ICD)-10 codes. Cardiac events were reported in phone call follow-ups and medical records or death certificates were obtained to prove the event by blinded investigators in the event committee.

### *Statistical analysis*

IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp) was used for data analysis. Continuous and categorical variables were reported as Mean  $\pm$  standard deviation (SD) and Frequency (percentage), respectively. Categorical variables were compared between the two groups using the chi-squared test or Fisher's exact test. The normality of continuous variables was tested using both the Kolmogorov-Smirnov test and visual assessment. Continuous variables with normal and non-normal distribution were compared using Student's t-test and Mann-Whitney U test, respectively. A step-wise logistic regression model was used to determine predictors of cardiac composite events (incidence of CVD, CVA, death due to cardiac causes, and all-cause mortality) in this study. The variables including OSA, age, gender, BMI, Current smoking, Diabetes, Hypertension, Dyslipidemia, CVD history, CVA history, and Follow-up duration were entered into the primary model. Finally, OSA, age, and CVD history remained in the

model. The significance level in this model was considered 0.2.

### *Sample size*

The sample size was calculated using the following formula introduced by Fleiss *et al.*<sup>15</sup>:

Considering 0.05 and 0.20 for  $\alpha$  and  $\beta$ , respectively, and 2.3% and 5.3% as the proportion of stroke in patients in the lower and upper AHI quartile according to Shahar *et al.*<sup>16</sup>, the minimum sample size was estimated to be  $n = 260$ . However, all 415 patients attending two sleep clinics in Isfahan, a central province of Iran, were enrolled in this study.

## **Results**

This study was conducted on 415 adults aged above 18 years with a history of snoring and/or witnessed apneas or other suspected sleep breathing disorders who underwent polysomnography, as shown in Figure 1. According to the results of polysomnography, 300 participants had  $AHI \geq 5$  and were categorized as OSA positive. Among participants with confirmed OSA diagnosis, 15 participants experienced cardiac events as defined previously. Four of these patients (27%), refuse to use non-invasive ventilation (NIV) (including continuous positive airway pressure (CPAP) or Bi-level Positive Airway Pressure (BIPAP), 6 patients (40%) used NIV incompletely, and 4 patients (27%) used CPAP or BIPAP completely. One of them did not answer the follow-up contact. Baseline characteristics, risk factors, and the follow-up duration of the participants are demonstrated in Table 1. Compared with subjects without OSA at baseline, the OSA patients were slightly older, and male-dominant, with a higher rate of HTN, dyslipidemia, and CVA history, and with a lower rate of smoking, DM, and CVD history. BMI and follow-up duration were also higher in OSA positive group. However, among all mentioned variables, a statistically significant difference was only observed for gender, BMI, smoking, dyslipidemia, and follow-up duration.

Cardiac composite events in each group are shown in Figure 2.

**Table 1.** Participants' Characteristics at Baseline

Characteristics	Total N=415	Positive OSA N=300	Negative OSA N=115	P value
Age: mean± SD	56.2 ±15.7	56.7 ± 15.0	54.8 ± 17.4	0.26*
Male: N (%)	211 (50.8)	166 (55.3)	45 (39.1)	0.003+
BMI: mean± SD	32.3 ±7.2	33.0 ± 7.1	30.7 ± 7.1	0.003*
Current smoking N (%)	43 (10.4)	14 (4.7)	29 (25.2)	< 0.001+
Diabetes: N (%)	47 (11.3)	30 (10.0)	17 (14.8)	0.16+
Hypertension: N (%)	153 (37.0)	118 (39.5)	35 (30.4)	0.08+
Dyslipidemia: N (%)	54 (13.0)	33 (11.0)	21 (18.3)	0.049+
CVD history: N (%)	14 (3.37)	8 (2.66)	6 (5.21)	0.22++
CVA history: N (%)	1 (0.24)	1 (0.33)	0 (0.0)	>0.99
Follow-up duration (months): median (IQR)	31 (19)	32 (14)	26 (23.0)	<0.001**

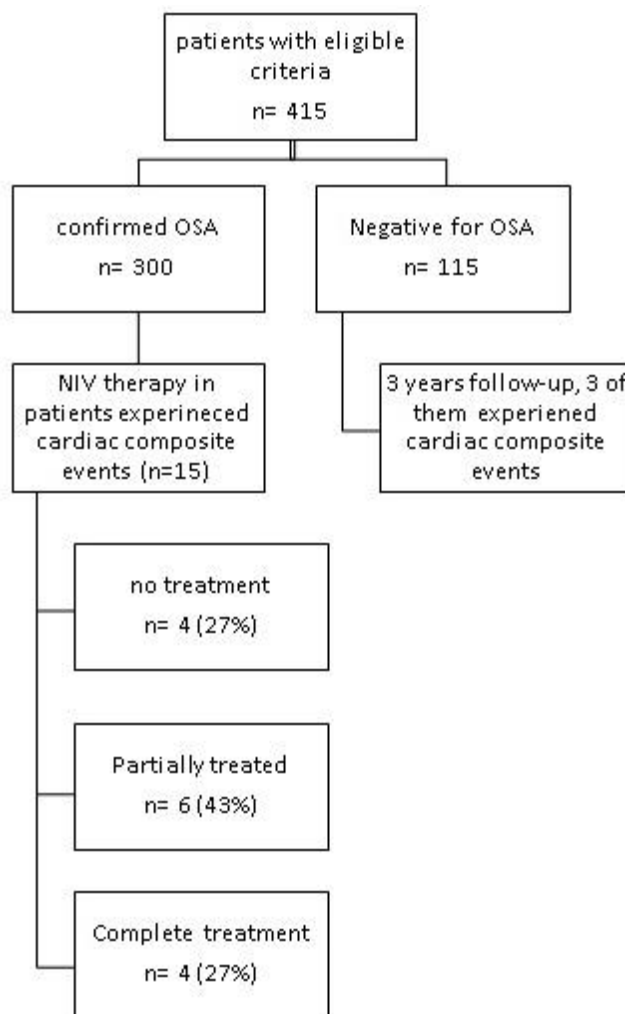
SD: standard deviation, CVD: cardiovascular disease, CVA: Cerebrovascular Accident, AHI: Apnea-Hypoxia Index, IQR: interquartile range

\*Independent t-test

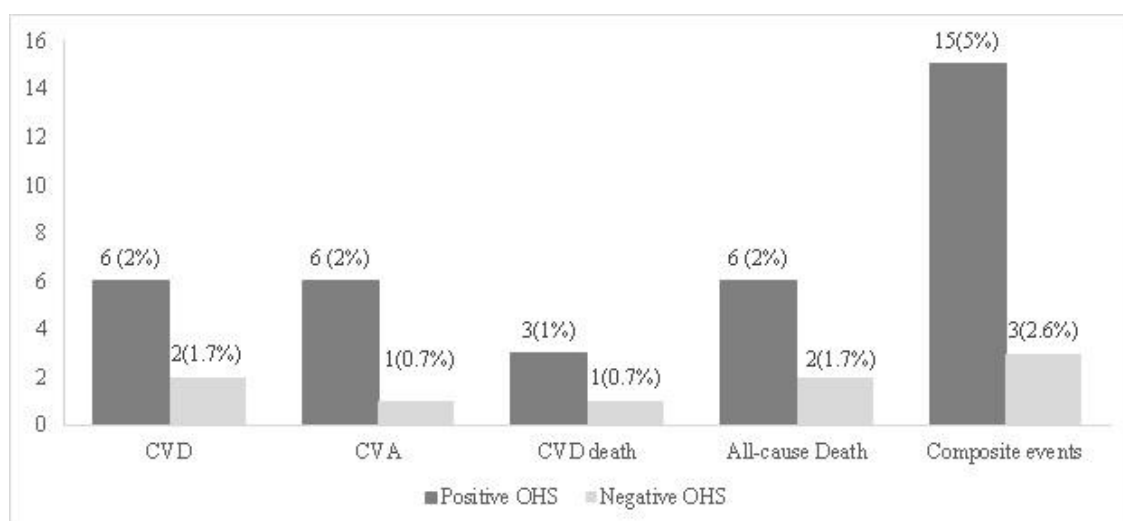
\*\*Mann-Whitney U test

+ Pearson Chi-Square test

++ Fisher's Exact Test



**Figure 1.** Participant's algorithm demonstrating the study cohort



**Figure 2.** Frequency of events according to OSA groups

Cardiac composite events occurred in 15 participants (5%) of the OSA positive group compared with 3 participants (2.6%) of the OSA negative group. In OSA negative group, one patient died due to CVA, and one patient died due to stent thrombosis. In OSA positive group, five patients were admitted due to cardiovascular diseases, one of whom underwent coronary artery bypass graft surgery. Six patients were admitted due to CVA,

and three of them died afterward (all-cause mortality). Three of the patients in the OSA positive group had sudden cardiac death. The incidence of CVD events was not significantly different between groups. The overall and in detail incidence of CVD events in OSA positive and negative groups are demonstrated in Table 2, reflecting no statistically significant differences between the two groups in terms of the incidence of each event.

**Table 2.** Comparison of events between positive and negative OSA patients

Group	Events									
	Composite events (CVA, CVD, Death)		CVD		CVA		Death due to any cause		Death due to CVD	
	Positive OSA (n=300)	Negative OSA (n=115)	Positive OSA (n=300)	Negative OSA (n=115)	Positive OSA (n=300)	Negative OSA (n=115)	Positive OSA (n=300)	Negative OSA (n=115)	Positive OSA (n=300)	Negative OSA (n=115)
Number (%) of patients with Events	15 (5.00)	3 (2.61)	6 (2.00)	2 (1.74)	6 (2.00)	1 (0.87)	6 (2.00)	2 (1.74)	3 (1.00)	1 (0.87)
P value*	0.284		0.863		0.423		0.863		0.903	

CVD: cardiovascular disease, CVA: cerebrovascular accident, OSA: obstructive sleeping apnea

\* Pearson Chi-Square test

Multiple logistic regression with a retrograde technique to determine predictors of cardiac composite events. OHS, age, gender, BMI, HTN, DM, dyslipidemia, smoking, CVD history, and follow-up duration variables were entered into the first model, and insignificant variables were removed one by one, considering a significant level lower than 0.2 ( $P < 0.2$ ). Finally, three variables including age, OHS, and

CVD history remained in the model (Table 3).

## Discussion

In the present prospective cohort study, the association between OSA and the incidence of cardiovascular events was investigated with three years of follow-up.

**Table 3.** Predictors of Composite events (CVA, CVD, and Death) according to multiple logistic regression

Variables	OR	P-value	Confidence Interval	
			Lower	Upper
OSA (yes)	2.43	0.188	1.02	5.76
Age (years)	1.03	0.091	1.01	1.06
CVD history (yes)	7.40	0.006	2.91	18.67

CVD: cardiovascular disease, CVA: cerebrovascular accident, OSA: obstructive sleeping apnea

\* significance level: P=value < 0.2

The main finding of this study was that OSA is a risk factor for cardiovascular events, increasing the odds of new cardiovascular events up to 2.41 at a 3 years follow-up period. Observational studies indicated that sleep apnea is associated with an elevated risk of serious cardiovascular events, including coronary artery disease, heart failure, stroke, and sudden death<sup>3, 16, 17</sup>. Data from over 6000 patients in the Sleep Heart Healthy Study revealed an independent association between OSA and the incidence of CAD, especially in patients with severe OSA. They reported the relative odds (95% Confidence Interval (CI)) of 2.38 (1.22-4.62), 1.58 (1.02- 2.46), and 1.27 (0.99-1.62) between OSA and heart failure, stroke, and coronary heart disease, respectively<sup>16</sup>. Another observational study on 1436 patients by Shah et al. reported a significant association between OSA and coronary artery events and cardiovascular death, after adjustment of traditional CVD risk factors, including HTN and obesity. OSA retained a statistically significant association with this composite outcome after adjustment for body mass index and hypertension (HR 2.06, 95% CI: 1.10-3.86, P = 0.024)<sup>18</sup>. A prospective study of patients with ACS with 227 days of follow-up showed that the incidence of major adverse cardiac events (cardiac death, re-infarction, and target vessel revascularization) was significantly higher in patients with OSA (23.5% vs 5.3%, P = 0.022)<sup>19</sup>. Another prospective study on 1927 men and 2495 women aged 40 years or greater with no history of coronary heart disease (CHD) and heart failure at baseline with a median follow-up of 8.7 years proved OSA as a significant independent predictor of incident heart failure in men but not in women

(adjusted hazard ratio: 1.58 for men with AHI  $\geq$  30 compared to men with AHI <5). A striking feature of this study is that the association of OSA with incident CHD and heart failure was observed in men but not in women<sup>16</sup>.

Several mechanisms may explain the association between OSA and cardiovascular disease. The mechanisms leading to atherosclerosis in OSA are related to the repeated hypoxic episodes which induce oxidative stress and intermittent hypoxia. Increased reactive oxygen species/reactive nitrogen species (ROS/RNS) and oxidative stress adversely affect the associated cardio/cerebrovascular disease<sup>20</sup>. Loss of endothelium-derived nitric oxide production and subsequent impairment of vascular relaxation inflammation and hypercoagulation has been reported in patients with OSA<sup>21</sup>.

On the other hand, OSA also affects other cardiac risk factors. OSA is not the most common cause of hypertension, but it is a well-recognized risk factor<sup>22</sup>. Various investigations have shown the synergistic effect of OSA and hypertension on CVD<sup>23</sup>. It has been revealed that smoking increases the risk of OSA and the severity of smoking is correlated with OSA severity and daytime sleepiness<sup>14, 24</sup>. A bidirectional link has been reported between OSA and types 2 DM. DM impaired the central control of respiration via diabetic neuropathy and consequently promotes the development of OSA. OSA also increases the incidence of type 2 DM<sup>11</sup>. Insulin resistance has been introduced as a potential mediator in OSA-related lipoprotein disturbances associated with enhanced CVD risk<sup>25</sup>. The combination of OSA with dyslipidemia exaggerates the adverse effects of OSA on the cardiovascular system,



which is more prominent among patients with severe OSA<sup>13</sup>.

### Strengths and Limitations

The present study was one of the few studies that assessed the causal link between OSA and CVD with a prospective cohort design. All sleep evaluations were conducted under the supervision of a board-certified sleep specialist. The other strength of the present study was three years of patient follow-up by staff that was blinded to the baseline and polysomnographic data. However, the present study had some limitations as well. First, the lower number of control groups was the main limitation of this study. Second, the lack of matching between the two groups due to heterogeneity and time differences may have affected the results. Third, due to technical difficulty, OSA severity and detailed parameters of polysomnography were not mentioned in the analysis. Finally, there is an inherent selection bias due to the observational nature of the study.

### Conclusion

OSA is a common health problem that may be considered an independent cardiovascular risk factor for CVD and a risk factor for cardiovascular events. It increased the odds of new cardiovascular events up to 2.41 at a 3 years follow-up period. In this study, OSA increased the risk of cardiovascular events by more than two-fold in patients with prior history of cardiovascular diseases. Thus, patients with OSA and prior history of CVD should be paid more attention to clinically.

### Author Contribution

SMAS wrote the proposal and collected data. SB substantially contributed to data collection and wrote the manuscript. AM analyzed data, interpreted the results, and critically revised the paper. JN and MB studied and revised the manuscript. BA and MEA facilitated data collection process. MKh read and revised the

manuscript. AKh planned the original study, supervised the study, and contributed to the conceptualization of the paper.

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