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Association of obstructive sleep apnea with all-cause and cardiovascular mortality: A population-based study

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Keywords:	obstructive sleep apnea, cardiometabolic diseases, hypertension, diabetes, cardiovascular diseases
Abstract:	Objectives: Obstructive sleep apnea (OSA) is one of the leading respiratory disorders, increasing the risk of cardiometabolic diseases. In the study, we investigated the association between OSA and the risk of cardiometabolic diseases and all-cause and cardiovascular mortality in adults. Methods: We made analysis based on National Health and Nutrition Examination Survey (NHANES) 2005-2008. The diagnosis of OSA was obtained from self-reported interviews. The baseline covariates were compared between participants with and without OSA status. Multivariable logistic regression was performed to explore the association between OSA and cardiometabolic diseases while multivariable Cox regression for all-cause and cardiovascular mortality. Results: OSA status was positively associated with higher risks of cardiometabolic diseases, including hypertension (odds ratio [OR] 1.28, 95% confidence interval [CI] 1.14-1.45; P < 0.001), diabetes (OR 1.46, 95%CI 1.22-1.76; P < 0.001) and cardiovascular diseases (OR 1.29; 95%CI 1.08-1.54; P = 0.006) after adjusting for numerous covariates. However, no associations of OSA with all-cause or cardiovascular mortality were observed. Conclusions: OSA was associated with a higher risk of hypertension, diabetes and cardiovascular diseases, while had no significant association with all-cause and cardiovascular mortality.

Association of obstructive sleep apnea with all-cause and cardiovascular mortality: A population-based study

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Abstract

Objectives: Obstructive sleep apnea (OSA) is one of the leading respiratory disorders, increasing the risk of cardiometabolic diseases. In the study, we investigated the association between OSA and the risk of cardiometabolic diseases and all-cause and cardiovascular mortality in adults.

Methods: We made analysis based on National Health and Nutrition Examination Survey (NHANES) 2005-2008. The diagnosis of OSA was obtained from self-reported interviews. The baseline covariates were compared between participants with and without OSA status. Multivariable logistic regression was performed to explore the association between OSA and cardiometabolic diseases while multivariable Cox regression for all-cause and cardiovascular mortality.

Results: OSA status was positively associated with higher risks of cardiometabolic diseases, including hypertension (odds ratio [OR] 1.28, 95% confidence interval [CI] 1.14-1.45; P < 0.001), diabetes (OR 1.46, 95%CI 1.22-1.76; P < 0.001) and cardiovascular diseases (OR 1.29; 95%CI 1.08-1.54; P = 0.006) after adjusting for numerous covariates. However, no associations of OSA with all-cause or cardiovascular mortality were observed.

Conclusions: OSA was associated with a higher risk of hypertension, diabetes and cardiovascular diseases, while had no significant association with all-cause and cardiovascular mortality.

Keywords: obstructive sleep apnea; cardiometabolic diseases; hypertension; diabetes; cardiovascular diseases

1 Introduction

Obstructive sleep apnea (OSA) is one of the sleep-related breathing disorders and repetitive episodes of upper airway obstruction results in reduced airflow, nocturnal hypoxemia and hypercapnia, arousals, sympathetic stimulation, and exaggerated intrathoracic pressure swings[1].The apnea-hypopnea index (AHI) is the most commonly used metric to determine the diagnosis and severity classification of OSA, as well as the associations between OSA and comorbidities.

Several studies have emphasized that OSA was an independent risk factor for coronary heart disease[2, 3], arrhythmia[4, 5], stroke[6, 7], and hypertension[8]. Metabolic disorders, including diabetes and impaired lipid metabolism, were also associated with OSA[9, 10]. Besides, OSA is a condition with potential for negative feedback in which it worsens conditions that may in turn worsen the OSA (eg, OSA → hypertension → worsened OSA). The underlying mechanisms are thought to include increased sympathetic nervous system activity, oxidative stress, and systemic inflammation. While OSA treatment with positive airway pressure is associated with a reduction in cardiovascular disease risk[11]. Previous studies found that OSA was reported to be associated with all-cause and cardiovascular mortality in patients with chronic obstructive pulmonary disease[12], acute coronary syndrome[13], and chronic kidney disease[14]. However, data on the link between OSA and mortality in general population was limited.

In the present study, we aimed to examine the association between OSA with all-cause and cardiovascular mortality in a nationally representative sample of the US population. It will improve our insights into the prevention and management of OSA.

2 Methods

2.1 Study population

We made a secondary analysis based on the National Health and Nutrition Examination Survey (NHANES) 2005-2008, a nationwidely multistage-sampling survey. Firstly, participants with missing data on OSA (n = 8310) and cardiometabolic diseases (n =1715) were excluded. Participants with cancer and pregnancy (n = 1279) and unavailable mortality status (n =11) were also excluded because pregnancy and cancer could have cofounding effect the sleep status and mortality respectively. A total of 9076 respondents were analyzed in this study (**Figure 1**). The study was approved by the Review Board of National Center of Health Statistics and the written consent was obtained from the participants.

2.2 Exposure and outcomes

The presence of OSA was determined through questionnaire that was administered by trained interviewers. Subjects who answered yes to the question "Have you ever been told by a doctor or other health professional that you have a sleep disorder?" and reported sleep apnea to "What was the sleep disorder?" were defined as having OSA[15].

Cardiovascular diseases consisting of congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke were obtained from the self-reports. The questions included "Has a doctor or other health professional ever told you that you have congestive heart failure /coronary heart disease/angina pectoris/heart attack/stroke?". Hypertension was diagnosed as the previous hypertension, or systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg, or taking antihypertensive drugs. Diabetes was diagnosed as previous diabetes or fasting glucose >7 mmol/L or HBA1c >6.5% or use of hypoglycemic drugs.

Mortality status was determined from the National Death Index by 31 December 2015. The ICD-10 codes for cardiovascular diseases included I00-I09, I11, I13, I20-I51, I60-I69 and I70-78.

2.3 Survey and measurement

A standard questionnaire was used to collect demographic information, including age, sex, race, educational level, poverty income ratio (PIR), body mass index (BMI), drinking and smoking status, history of diseases (hypertension, diabetes and cardiovascular disease) and history of medication (antihypertensive drug, hypoglycemic drug and lipid-lowering drug). Smoking was categorized into current, former and never. Race/ethnicity was divided into four groups: non-Hispanic white or black, Mexican American and Others. Education level included four categories: less than or equivalent high school, college or above. Height and weight were measured by physical examinations, and BMI was calculated as body weight divided height squared. Serum levels of cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were measured using by an enzymatic assay. Estimated glomerular filtration rate (eGFR) was calculated based on CKD-EPI equation.

2.4 Statistical analysis:

Numeric parameters were expressed as the mean ± standard deviation and categorical variables were presented as numbers (percentages). Differences between groups was compared using analysis of variance for quantitative values and Chi-squared test for qualitative parameters. Multivariable logistic regression analysis was used to explore the cross-sectional relationship between OSA with cardiometabolic diseases. Multivariable Cox regression was performed to explore the prognostic effect of OSA in all-cause and cardiovascular mortality. Model 1 was unadjusted; Model 2 was adjusted for gender, and age. Model 3 was adjusted for Model 2

covariates plus race, education, PIR, BMI, drinking, smoking, and activity. Model 4 was adjusted for Model 3 covariates plus medications use and cholesterol, triglycerides, HDL, LDL, and eGFR. All statistical analysis was performed using IBM SPSS 25.0. P value < 0.05 was deemed as statistically significant.

3 Results

9076 individuals were included in our study. Compared to participants without OSA, population with OSA tend to be young, female and non-Hispanic white, and had more percentage of diabetes, hypertension, and cardiovascular disease. Cholesterol, LDL-C and eGFR were lower among participants with OSA **(Table 1).**

To investigate the association between OSA and cardiometabolic diseases (hypertension, diabetes and cardiovascular diseases), we established multiple logistic regression models shown in **Table 2.** OSA was positively associated with higher odds of hypertension (OR = 1.44; 95%CI, 1.29, 1.60; P < 0.001), diabetes (OR = 1.86; 95%CI, 1.65, 2.09; P < 0.001) and cardiovascular diseases (OR = 1.54; 95%CI, 1.32, 1.80; P < 0.001) in Model 1. This association was not altered after adjusting for gender, age, race, education, PIR, BMI, drinking, smoking, activity, hypertension, diabetes, CVD, antihypertensive drugs, hypoglycemic drugs, lipid-lowering drugs, cholesterol, triglycerides, HDL, LDL, and eGFR in Model 4. Furthermore, we investigated the association between OSA with all-cause and cardiovascular mortality. Multivariable Cox regression analysis found that OSA had no significant association with all-cause and cardiovascular mortality in all models **(Table 3)**.

4 Discussion

Our study concluded that OSA was associated with the presence of cardiometabolic diseases, including diabetes, hypertension and cardiovascular diseases, while had no significant relationship with all-cause and cardiovascular mortality.

In according to our results that OSA increased the risk of cardiovascular diseases. Punjabi et al. showed that severe hypopneas were independently associated with cardiovascular diseases[16]. Sarah et al conducted a longitudinal study showing that hypertension was related to OSA during rapid eye movement sleep during community-dwelling men[17]. OSA and diabetes also has been known to be closely related to each other[10].The prevalence of OSA in people with type 2 diabetes mellitus was higher than the general population[18]. The underlying mechanism might be that OSA induced intermittent hypoxia and arousals, which may result in decreased insulin sensitivity, sympathetic excitation, and systemic inflammation that eventually leaded to diabetes[19-21]. Our study was in consistent with previous results and found OSA was associated with the presence of cardiometabolic diseases. OSA and cardiovascular disease may share multiple common risk factors, including obesity, male sex, and older age. Besides, the mechanisms underlying this association are thought to include increased sympathetic nervous system activity, oxidative stress, and systemic inflammation, with these effects mediated in part by elevated blood pressure and impaired glucose metabolism.

Recent study showed that hypoxemic burden due to sleep apnea was strongly predictive of cardiovascular diseases related mortality[22]. Lavie et al. conducted a large prospective cohort study and concluded that severe OSA increased the risk of mortality in middle-aged male

patients[23]. Marin et al. also concluded that those with severe OSA were at higher risk for both fatal and non-fatal cardiovascular events[24]. However, we found OSA had no significant relationship with all-cause and cardiovascular mortality. The difference could be due to the fact that OSA diagnosis was based on patient self-reports rather than objective tests. The underlying reasons need further investigations.

Our study has some strengths. Firstly, our association was robust after adjusting so many covariates, which was not included in previous studies. Besides, our sample was relatively large. Some limitations also existed in our study. First, some variables were based on questionnaires. Secondly, OSA was not diagnosed by polysomnography and therefore the prevalence of OSA could be overestimated.

5 Conclusion

In conclusion, we found that OSA was associated with the presence of cardiometabolic diseases, including diabetes, hypertension and cardiovascular diseases. However, it could not predict the mortality in general population.

List of abbreviations

OSA, Obstructive sleep apnea;

NHANES, National Health and Nutrition Examination Survey;

OR, odds ratio;

CI, confidence interval;

AHI, apnea-hypopnea index;

NCHS, National Center of Health Statistics;

PIR, poverty income ratio;

BMI, body mass index;

HDL-C, high density lipoprotein cholesterol;

LDL-C, low density lipoprotein cholesterol;

eGFR, estimated glomerular filtration rate;

Declarations

Ethics approval and consent to participate

The study was approved by the Review Board of National Center of Health Statistics and the written consent was obtained from the participants.

Consent for publication

Not applicable.

Availability of data and materials

All data could be obtained upon request from Xuanfeng Zhu.

Competing interests

The authors have nothing to disclose.

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None.

Author contribution

ZXF and LJN designed this study; GJ, SLC and SM performed the statistical analysis; GHM and

GJH wrote the manuscript; ZDD and WWJ prepared the tables and figures.

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Table 1. Baseline variables of the study participants according to OSA status.

Variables	OSA (n=4648)	No OSA (n=4428)	P
Male	1915 (43.2)	2725 (58.6)	<0.001
Age, years	56.84 (9.09)	59.99 (6.26)	<0.001
Race (%)			
Non-Hispanic white	2042 (46.1)	2130 (45.8)	0.416
Non-Hispanic black	1009 (22.8)	1028 (22.1)	
Mexican American	857 (19.4)	892 (19.2)	
Others	520 (11.7)	598 (12.9)	
Education (%)			
Less than high school	1293 (29.2)	1398 (30.1)	0.002
High school or equivalent	1018 (23.0)	1188 (25.6)	
College or above	2111 (47.7)	2057 (44.3)	
PIR (%)			
<1	849 (20.8)	780 (17.9)	0.003
1~3	1714 (42.0)	1850 (42.6)	
>3	1521 (37.2)	1716 (39.5)	
BMI, kg/m2	27.14 (5.73)	30.55 (7.25)	<0.001
Drinking (%)	578 (48.4)	632 (57.0)	<0.001
Smoking (%)			
Current	773 (22.2)	987 (28.8)	<0.001
Past	168 (4.8)	182 (5.3)	
Never	2543 (73.0)	2257 (65.9)	
Activity (%)			
Vigorous	1166 (44.2)	1182 (43.3)	0.52
Moderate	1089 (41.3)	1168 (42.8)	
Inactive	381 (14.5)	378 (13.9)	
Past history (%)			
HBP	658 (16.6)	955 (22.3)	<0.001
DM	497 (11.2)	884 (19.0)	<0.001
CVD	288 (6.5)	450 (9.7)	<0.001
Prior medication (%)			
Antihypertensive drug	986 (85.2)	1536 (86.5)	0.343
Hypoglycemic drug	292 (53.1)	507 (56.1)	0.29
Lipid-lowering drug	541 (80.6)	849 (81.1)	0.861
Cholesterol, mg/dL	196.95 (40.72)	199.09 (42.78)	0.021
Triglycerides, mg/dL	144.45 (122.20)	173.82 (148.55)	<0.001
HDL, mg/dL	55.11 (16.11)	50.33 (15.56)	<0.001
LDL, mg/dL	113.00 (34.81)	116.14 (35.90)	0.006
eGFR, ml/min per 1.73 m2	91.05 (25.24)	89.49 (24.42)	0.005

Data are presented as mean (SD) or n (%). PIR, poverty income ratio; BMI, body mass index; HBP, high blood pressure; DM, diabetes mellites; CVD, cardiovascular diseases; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate.

Table 2. Association of OSA with cardiometabolic diseases.

Cardiometabolic diseases	OR	95% CI	P
Hypertension			
Model 1	1.44	[1.29, 1.60]	<0.001
Model 2	1.37	[1.22, 1.54]	<0.001
Model 3	1.30	[1.15, 1.46]	<0.001
Model 4	1.28	[1.14, 1.45]	<0.001
Diabetes			
Model 1	1.86	[1.65, 2.09]	<0.001
Model 2	1.85	[1.63, 2.09]	<0.001
Model 3	1.37	[1.20, 1.57]	<0.001
Model4	1.46	[1.22, 1.76]	<0.001
Cardiovascular diseases			
Model 1	1.54	[1.32, 1.80]	<0.001
Model 2	1.51	[1.28, 1.79]	<0.001
Model 3	1.36	[1.14, 1.62]	0.001
Model 4	1.29	[1.08, 1.54]	0.006

Model 1: unadjusted.

Model 2: adjusted for gender, and age.

Model 3: adjusted for gender, age, race, education, PIR, BMI, drinking, smoking, and activity.

Model 4: adjusted for gender, age, race, education, PIR, BMI, drinking, smoking, activity, antihypertensive drugs, hypoglycemic drugs, lipid-lowering drugs, cholesterol, triglycerides, HDL, LDL, and eGFR.

Table 3. Association of OSA with all-cause and cardiovascular mortality.

	HR	95% CI	P
All-cause mortality			
Model 1	0.93	[0.82, 1.04]	0.206
Model 2	0.97	[0.86, 1.10]	0.634
Model 3	0.99	[0.87, 1.12]	0.886
Model 4	0.96	[0.84, 1.09]	0.507
Cardiovascular mortality			
Model 1	0.96	[0.72, 1.28]	0.787
Model 2	0.94	[0.70, 1.25]	0.658
Model 3	0.94	[0.70, 1.27]	0.685
Model 4	0.91	[0.67, 1.23]	0.532

Figure 1. The flow chart of participant selection.

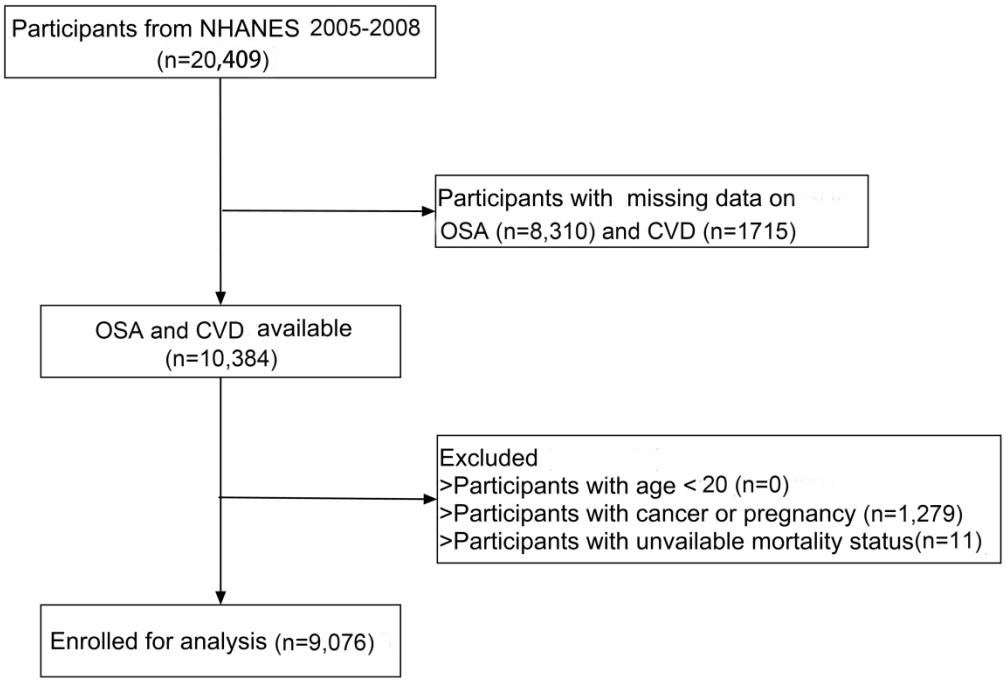

Figure 1. The flow chart of participant selection.