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Association between Obstructive Sleep Apnea and Intracranial Artery Calcification Stratified by Gender and Body Mass Index: A Hospital-Based Observational Study

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Keywords
Intracranial artery calcification · Obstructive sleep apnea · Computed tomography · Body mass index · Apnea-hypopnea index

Abstract

Background and Objectives: Obstructive sleep apnea (OSA) is an independent risk factor for stroke. Furthermore, intracranial arterial calcification (IAC) has been validated as a marker for subclinical cerebrovascular disease. However, the relationship between OSA with IAC was less studied compared with its established association with coronary artery calcification. In this study, we aimed to investigate the association between the severity of OSA and the degree of IAC in hospitalized patients without preexisting cardiovascular disease. ***Methods:*** This hospital-based observational study was conducted from June 1, 2017, to May 1, 2019. In total, 901 consecutive patients who underwent head computed tomography scans and portable sleep monitoring were included. On the basis of the apnea-hypopnea index (AHI), patients were divided into four OSA severity groups (normal: AHI <5/h; mild: 5≤ AHI <15/h; moderate: 15≤ AHI <30/h; severe: AHI ≥30/h). Associations of OSA with IAC scores were assessed by using multivariate logistic regression analysis. ***Results:*** Of the 901 patients, 484 (53.7%) were men; the mean (SD) age was 66.1 (10.0) years. The non-OSA group included 207 (23.0%) patients; mild OSA, 209 (23.2%); moderate OSA, 235 (26.1%); and severe OSA, 169 (18.8%). Mean IAC scores were higher in the severe OSA group compared with non-, mild, and moderate OSA groups (4.79 vs. 2.58; 4.79 vs. 2.94; 4.79 vs. 3.39; $p < 0.001$). Multivariate analysis adjusted for confounding factors revealed that only severe OSA was associated with a higher IAC score (odds ratio [OR]: 1.65; 95% confidence interval [CI]: 1.43–1.91; $p < 0.001$). In stratified analyses by BMI, among participants with a BMI <25 kg/m^2, the positive association between AHI values and IAC scores was found in the moderate OSA group (OR: 1.23; 95% CI: 1.05, 1.43; $p = 0.01$) and the severe OSA group (OR: 1.96; 95% CI: 1.55, 2.48; $p < 0.001$). When stratified by gender, in women, the positive association was found in the moderate OSA group (adjusted OR: 1.21; 95% CI: 1.02–1.51; $p = 0.016$) and the severe OSA group (adjusted OR: 1.76; 95%

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CI: 1.36–2.25; $p < 0.001$). For the men group, a positive association between IAC scores and AHI was only observed in the severe OSA group. ***Discussion:*** These findings suggest that OSA, in particular severe OSA (AHI ≥30), is independently associated with higher IAC scores. Women and no-obesity individuals appeared more susceptible to adverse OSA-related subclinical cerebrovascular disease as measured by IAC scores.

Introduction

Intracranial arterial calcification (IAC), a frequent finding on head computed tomography (CT) scans, have been established to be an independent predictor of adverse clinical outcomes including ischemic stroke, cerebral small vessel disease, and cognitive impairment [1–4]. Previously considered as a proxy of atherosclerosis, vascular calcification shares some traditional cardiovascular risk factors with other atherosclerotic diseases, such as age, smoking, hypertension, and diabetes [5–9]. In recent years, with the in-depth research of IAC, new risks have emerged and have been identified, which might lead to new therapeutic options for prevention of cerebrovascular diseases.

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse during sleep resulting in intermittent hypoxemia and sleep fragmentation, with an approximate prevalence ranging from 9% to 38% of the general population [10]. Early observational studies indicated a high prevalence of OSA in patients with cardiovascular disease (CVD), although a causal association was unclear and underlying mechanisms remains incompletely understood. In coronary artery disease studies, previous studies have demonstrated an association between OSA and increased coronary artery calcification (CAC), which is a surrogate marker for subclinical atherosclerosis [11–14]. So far, however, the association between OSA and vascular calcification in the intracranial arteries, both highly prevalent among older adults, has been investigated by very few studies [15]. To better understand the relation between OSA and cerebrovascular diseases, examining the association between OSA and subclinical cerebral atherosclerotic changes may be valuable. Furthermore, OSA is a heterogeneous disorder with physiological and polysomnographic differences between obesity categories and gender [16, 17]; however, whether gender and obesity modify the risk of IAC in patients with OSA is uncertain.

In the present hospital-based study, we aimed to investigate the association of risk of OSA with IAC in patients with no previous history of CVD. We also assessed the relationships between OSA and IAC in different gender and obesity groups.

Methods

The study protocol was approved by the Clinical Ethics Committees of the participating hospitals. This cross-sectional study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (online suppl. 1; for all online suppl. material, see https://doi.org/10.1159/000533843).

Study Participants

This retrospective study included consecutive patients who underwent both head CT scans and portable sleep monitoring from June 1, 2017, to May 1, 2019. The inclusion criteria were age ≥18 years and have performed both head CT scans and sleep monitoring. The exclusion criteria were as follows: (1) obviously poor image quality; (2) insufficient clinical data; (3) inadequate period of sleep (<2 h); (4) subjects with known sleep disorders and breathing on continuous positive airway pressure; (5) history of CVD; (6) gastric tube or endotracheal tube insertion. The following data were obtained from the electronic medical records: clinical demographic factors, including age and sex; blood tests included total cholesterol (TC), low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol (HDL-C), triglyceride (TG), hemoglobin A1c, homocysteine (Hcy); height; weight; smoking status; alcohol drinking; past medical history; and treatment.

Obesity was defined as BMI ≥25 kg/m^2 based on the cutoffs for Asian population as recommended by the WHO. Hypertension was defined as systolic blood pressure above 140 mm Hg or diastolic blood pressure of ≥90 mm Hg or a history of hypertension. The diagnosis of diabetes mellitus was based on a 75 g oral glucose tolerance test or as hemoglobin A1c ≥6.0% or a history of diabetes.

Image Acquisition and IAC Assessment

CT imaging was performed by using a 64-row multidetector CT scanner without contrast administered. The patient's head is positioned to achieve a standard axial plane with tilting along the occipital-mental line, ensuring coverage of every region from skull base to the vertex. Two readers who were blinded to clinical information of patients independently evaluated the CT images by visual analysis.

The severity of IAC was assessed using visual grading scales. Major intracranial artery segments (internal carotid artery [ICA] C3–C7 segments, M1 segment of middle cerebral artery, V4 segments of vertebral artery, and basilar artery) were assessed. The presence of IAC was defined as hyperdense foci over 130 Hounsfield units. As the established IAC scoring method described in our previous study [18, 19], an overall CT score of 0–2, 3–5, and 6–8 was considered as mild, moderate, and severe degrees of IAC, respectively.

OSA Examination

The diagnosis of OSA was assessed using a portable device testing, a validated portable respiratory monitor that records apneas and oxygen saturation. All recordings were undertaken at the hospital under the control of a sleep technologist. Apnea was defined as a total absence (>90%) and hypopneas as a decrease in nasal flow for ≥10 s, accompanied by at least 3% decreased in blood oxygen saturation, respectively. The apnea-hypopnea index (AHI) was calculated by dividing the total number of apneas and hypopneas by total time in bed. The OSA was defined as an AHI ≥5 events/hr of greater than or equal to 5 per hour. OSA severity was graded as mild (AHI 5–15/h), moderate (AHI 15–30/h), and severe (AHI >30/h), in accordance with previous reports. Automated analysis was verified by an investigator experienced with the technique and who was blinded to other clinical data.

Statistical Analysis

Baseline demographic factors, clinical characteristics, and laboratory tests findings were compared between four AHI groups. Continuous data were presented as mean ± SD for normally distributed data, and categorical variables were shown as frequencies (%). Continuous variables were compared using ANOVA if data are normally distributed or the Kruskal-Wallis test when data are not normally distributed. Categorical variables were compared using the χ^2 test. Multiple comparisons were used for pairwise comparisons of IAC values in the four OSA groups. Multivariate regression analysis was further used to investigate the independent variables. Covariates selected for further analysis were the variables with significant differences between groups in the clinical analysis and their biological importance as cerebrovascular risk factors. We progressively tested three models independently for OSA and IAC: model 1: adjusted for BMI; model 2: further adjusted for sex; model 3: model 2 plus age, current smoking, current alcohol use, hypertension, diabetes, TG, TC, LDL, HDL, Hcy. Multiple imputation was used to handle patients with missing clinical data. For all statistical tests, A 2-sided $p < 0.05$ was statistically significant. All statistical analyses were performed using the SPSS software version 26 (IBM, Chicago, IL, USA).

Results

Baseline Characteristics of the Study Sample

A total of 1,076 patients with head CT scans and sleep monitoring were initially included. The following number of patients were excluded: 26 patients with poor CT imaging quality and 33 patients with inadequate period of sleep (<2 h), 106 patients for a history of CVD, 4 patients for insufficient data, and 6 patients for being gastric tube or endotracheal tube insertion. A total of 901 participants were included in the final analysis (Fig. 1). The mean age of the 901 patients was 66.1 ± 10.0 years, and 53.7% were male. A total of 694 individuals (77.0%) were diagnosed with OSA according to AHI criteria. Within this OSA group, 290 (32.2% of the complete study sample) had mild, 235 (26.1%) had moderate, and 169 (18.7%) had severe OSA. The characteristics of the studied population according to OSA severity are listed in Table 1. There was a significant difference in age, gender, BMI, Hcy, history of hypertension or diabetes among the four AHI groups ($p < 0.001$). However, there were no differences in smoking or alcohol status, TC, low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol, and TG among the four groups (all, $p > 0.05$).

Association of OSA with IAC Scores

Mean IAC scores were higher in the severe OSA group compared with non-, mild, and moderate OSA groups (4.79 vs. 2.58; 4.79 vs. 2.94; 4.79 vs. 3.39; $p < 0.001$); There was also a significant difference in IAC scores between the moderate OSA group and the normal group ($p = 0.001$) (Fig. 2). Using the non-OSA group as a reference, in the unadjusted model, odds ratio (OR) for IAC scores was 1.08 (95% confidence interval [CI]: 1.00, 1.18) in the mild OSA group, 1.18 (95% CI: 1.08, 1.30) in the moderate OSA group, and 1.66 (95% CI: 1.47, 1.87) in the severe OSA group. After adjusting for BMI (model 1) and additionally adjusting for sex (model 2), the association remained significant in the moderate or severe OSA group (both $p < 0.05$). After further accounting for other variables in model 3, the associations between the severity of OSA and IAC scores were attenuated in the severe OSA group but remained significant (OR: 1.65; 95% CI: 1.43, 1.91) ($p < 0.001$) (Table 2).

Multivariate models (Table 3) showed that age ($p < 0.001$), male sex ($p = 0.009$), hypertension ($p = 0.004$), and moderate-severe OSA ($p = 0.024$) were risk factors for IAC in the group with a score 3–5, when the group with an IAC score of 0 was considered as the reference. Similarly, age ($p < 0.001$), male sex ($p = 0.027$), hypertension ($p = 0.001$), and moderate-severe OSA (adjusted OR: 2.60; 95% CI: 1.35, 4.99; $p = 0.004$) were risk factors for the group with an IAC score 6–8.

Association between OSA and IAC Scores Stratified by BMI and Gender

Table 4 displays the results of the stratified analyses by BMI. Among participants with a BMI ≥25, in fully adjusted model, AHI was not independently related to IAC scores in all three OSA severity groups. Conversely, among participants with a BMI <25, the positive association between AHI values and IAC scores was found in the moderate OSA group (OR: 1.23; 95% CI: 1.05, 1.43; $p = 0.01$) and the severe OSA group (OR: 1.96; 95% CI: 1.55, 2.48; $p < 0.001$).

Table 5 demonstrates the association between OSA severity and IAC scores stratified by gender. In women, 15 ≤ AHI <30 (compared to AHI <5) was associated with

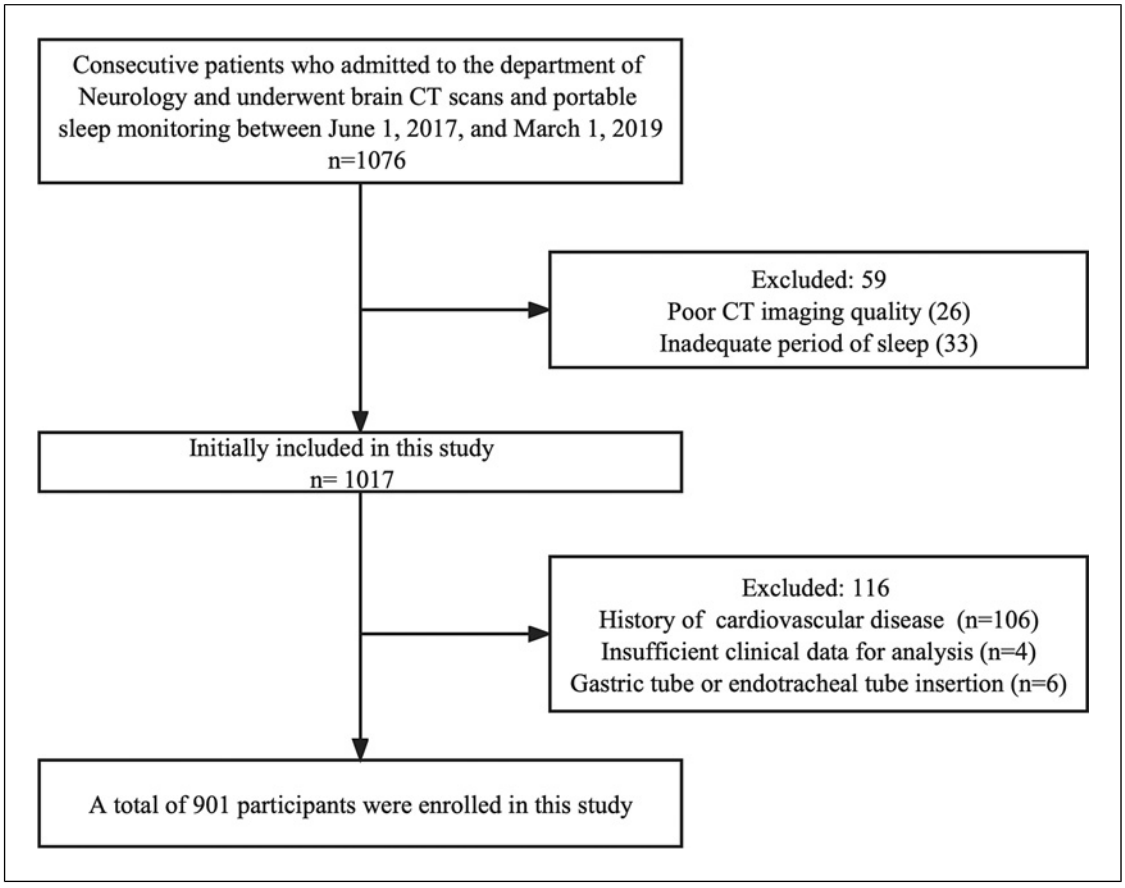

Fig. 1. Flowchart of study participant exclusion criteria in this study.

1.2-fold odds of having higher IAC scores (adjusted OR: 1.21; 95% CI: 1.02–1.51; $p = 0.016$), the positive association was also found in the severe OSA group (adjusted OR: 1.76; 95% CI: 1.36–2.25; $p < 0.001$), and no significant association was observed in participants with 5 ≤ AHI <15. For the men group, a positive association between IAC scores and AHI was only observed in participants with AHI ≥30.

Discussion

This study found positive, statistically significant associations between IAC scores and severe OSA (AHI ≥30), in adults with suspected OSA. The association remained significant after thorough adjustment for additional confounding factors, indicating a strong, independent link between the two variables. Of interest, we observed that the effect of OSA on IAC would be stronger among nonobese and women participants.

OSA have been reported to be associated with arterial calcification in different populations but mainly focus on CAC. In a cross-sectional study of 202 patients without clinical coronary disease, Sorajja et al. [20] found that the presence of OSA was independently associated with the presence and degree of CAC. Another prospective cohort study that included 2,603 participants showed that OSA was associated with CAC score progression after adjustment for demographics and BMI. However, the results were attenuated after adjustment for traditional CVD risk factors [13]. Similar to the correlation between OSA and arterial calcification in other locations, IAC may be associated with OSA. However, few studies have investigated the relationship between the two variables [15, 21]. In the present study, we revealed that severe OSA was independently associated with higher IAC scores in a large sample of adults. This finding is consistent with a previous study investigating 73 ischemic stroke patients in the ICA territory due to large-artery atherosclerosis, which found that the

Table 1. Baseline characteristics of study participants

Characteristics	No OSA (*n* = 207)	Mild OSA (*n* = 290)	Moderate OSA (*n* = 235)	Severe OSA (*n* = 169)	*p* value
Age, years	63.72±9.48	65.96±9.75	67.90±9.74	69.13±10.60	<0.001
Male, *n* (%)	89 (43.00)	151 (52.07)	132 (56.17)	112 (66.27)	<0.001
Current smoking, *n* (%)	30 (14.50)	50 (17.24)	51 (21.70)	31 (18.34)	0.247
Current drinking, *n* (%)	13 (6.28)	19 (6.55)	16 (6.81)	11 (6.51)	0.997
SBP, mm Hg	138.06±20.31	140.13±19.90	143.99±20.47	144.82±20.23	0.001
DBP, mm Hg	81.99±12.64	84.34±12.10	85.81±12.54	85.34±12.60	0.006
BMI, kg/m^2	23.64±4.37	24.10±3.61	24.20±3.63	25.13±4.12	<0.001
AHI, mean (SD)	2.25±1.45	9.51±2.89	21.46±3.88	42.49±12.84	<0.001
Min Sao_2, %	89.53±4.10	86.25±5.35	84.06±5.88	85.40±7.89	<0.001
IAC scores, mean (SD)	2.58±2.21	2.94±2.15	3.39±2.10	4.79±2.08	<0.001
Blood test, mean (SD)					
TCH, mmol/L	4.67±1.20	4.54±1.03	4.69±1.25	4.47±1.25	0.105
HDL-C, mmol/L	1.14±0.29	1.13±0.30	1.13±0.28	1.09±0.27	0.295
LDL-C, mmol/L	3.08±1.05	2.99±0.94	3.07±1.11	2.83±1.02	0.058
TG, mmol/L	1.51±0.85	1.51±1.00	1.56±1.23	1.57±0.98	0.906
HbA1c, %	6.11±1.22	6.13±1.21	6.22±1.39	6.31±1.32	0.062
Hcy, μmol/L	10.13±3.35	10.91±4.16	11.52±4.81	12.24±4.47	<0.001
Medical history, *n* (%)					
Hypertension	102 (49.28)	170 (58.62)	152 (64.68)	104 (61.54)	0.009
Diabetes	42 (20.29)	58 (20.00)	47 (20.00)	53 (31.36)	0.018

Categorical variables are shown as number (percentage); continuous variables as mean ± standard deviation. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; Hcy, homocysteine; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density-lipoprotein cholesterol.

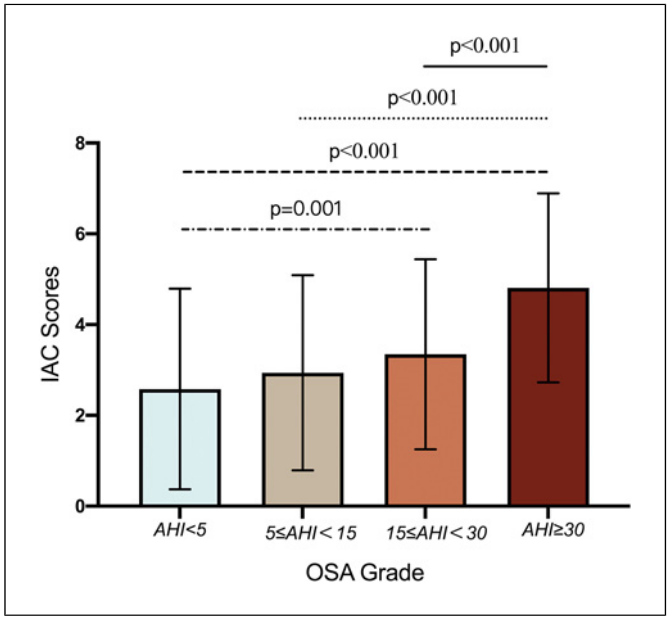

Fig. 2. Differences in IAC scores by the OSA grades.

presence of ICA calcification was related to high risk for OSA. Of note, the sample size was fairly small in that study, and the risk for OSA was assessed using the Berlin Questionnaire, which may limit the validity and generalizability of their findings [15].

OSA is characterized by recurrent episodes of complete or partial airway obstruction, resulting in intermittent hypoxia and reoxygenation to body tissues and organs, which could contribute to artery calcification through direct and indirect mechanisms. First, OSA-chronic intermittent hypoxia could promote oxidative stress by increasing reactive oxygen species expression, inflammation by increasing NF-κB activity, and BP elevation by an increase in sympathetic activity and ultimately the formation of artery calcification or causing damage to multiple systems [22–24]. Additionally, artery calcification progression could occur through OSA indirect mechanisms. Patients with OSA usually have several comorbidities, such as hypertension, obesity, diabetes, and hyperlipidemia, which are all proven common risk factors for IAC [25–28].

In the present study, we found that women tend to have a lower AHI than males, which was consistent with most of the previous studies [29, 30]. Noteworthily, in women, we found a high risk of IAC in patients with moderate/severe OSA, suggesting that women may be more susceptible than men to some cerebrovascular disorders caused by OSA [12]. Although the underlying

Table 2. Multiple analyses of AHI and IAC scores

AHI/h	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
AHI <5	Ref	Ref	Ref	Ref
5≤ AHI <15	1.08 (1.00, 1.18)	1.02 (1.00, 1.07)	1.06 (0.97, 1.16)	1.05 (0.95, 1.16)
15≤ AHI <30	1.18 (1.08, 1.30)[a]	1.16 (1.06, 1.28)[a]	1.15 (1.04, 1.27)[a]	1.11 (1.00, 1.24)
AHI ≥30	1.66 (1.47, 1.87)[a]	1.71 (1.50, 1.96)[a]	1.69 (1.48, 1.94)[a]	1.65 (1.43, 1.91)[a]

Model 1: adjusted for BMI. Model 2: further adjusted for gender. Model 3: further adjusted for age, current smoking, current alcohol use, history of CAD, history of hypertension, history of diabetes, TG, TC, LDL, HDL, Hcy. [a]$p < 0.05$.

Table 3. Multivariate analysis to identify factors associated with IAC degrees compared with the group with an IAC score of 0

Characteristic	IAC scores		
	1–2	3–5	6–8
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age	1.07 (1.03, 1.10)[a]	1.08 (1.06, 1.11)[a]	1.14 (1.10, 1.19)[a]
Male sex	1.37 (0.81, 2.31)	1.79 (1.16, 2.77)[a]	2.09 (1.09, 4.02)[a]
BMI	1.02 (0.96, 1.09)	1.04 (0.99, 1.10)	1.03 (0.96, 1.12)
Hypertension	1.21 (0.70, 2.08)	1.97 (1.25, 3.11)[a]	3.07 (1.56, 6.04)[a]
Diabetes	1.58 (0.79, 3.16)	1.37 (0.76, 2.47)	1.95 (0.89, 4.26)
Moderate-severe OSA	0.93 (0.52, 1.65)	1.69 (1.07, 2.66)[a]	2.60 (1.35, 4.99)[a]

[a]$p < 0.05$.

Table 4. Logistic regression analysis of IAC scores in relation to AHI stratified by BMI

AHI score, compared to AHI <5/h	AHI/h	OR[a]	95% CI	*p* value
BMI <25 kg/m^2	5 ≤AHI <15	1.09	(0.95, 1.25)	0.23
	15 ≤AHI <30	1.23	(1.05, 1.43)	0.01
	AHI ≥30	1.96	(1.55, 2.48)	<0.001
BMI ≥25 kg/m^2	5 ≤AHI <15	1.04	(0.85, 1.26)	0.72
	15 ≤AHI <30	1.09	(0.89, 1.32)	0.42
	AHI ≥30	1.20	(0.98, 1.08)	0.10

[a]Adjusted for age, gender, current smoking, current alcohol use, history of CAD, history of hypertension, history of diabetes, TG, TC, LDL, HDL, Hcy.

Table 5. Multivariate regression analysis: association between IAC scores and AHI, stratified by gender

AHI categories/h	Women (*n* = 417)		Men (*n* = 484)	
	adjusted OR (95% CI)	*p* value	adjusted OR (95% CI)	*p* value
AHI <5	1	—	1	—
5 ≤AHI <15	0.93 (0.80, 1.12)	0.864	1.15 (0.94, 1.32)	0.079
15 ≤AHI <30	1.21 (1.02, 1.51)	0.016	1.08 (0.94, 1.35)	0.145
AHI ≥30	1.76 (1.36, 2.25)	<0.001	1.52 (1.29, 2.04)	<0.001

Adjusted for age, BMI, current smoking, current alcohol use, history of CAD, history of hypertension, history of diabetes, TG, TC, LDL, HDL, Hcy.

physiological mechanisms are still not clearly defined, the endothelial dysfunction caused by OSA is among those suspected. Compared with men, women with OSA reportedly have more endothelial dysfunction and are more likely to develop hypertension and insulin resistance [31, 32]. In addition, previous studies have shown that, with equivalent AHI, C-reactive protein and fibrinogen levels were higher in women compared with men, suggesting that sex-different inflammatory response to OSA may be another key factor [33–36].

Our data showing that nonobese patients tend to have less severe OSA compared with obese patients are consistent with previous reports [37, 38]. Moreover, the current findings also suggest that sleep apnea, especially moderate to severe OSA (AHI ≥15), is independently associated with IAC, mainly in nonobese individuals. These results provide an important additional insight into the relationship between obesity, OSA, and artery calcification. OSA and obesity frequently coexist, and each one is strongly linked to the development of artery calcification. In a large sample undergoing CAC scoring, the odds of CAC were increased in those overweight and obese participants compared with those with normal BMI, even after adjustment for traditional risk factors [39]. Results from community-based studies also shown positive association between AHI severity and CAC; however, additional adjustment for BMI reduced the association to a nonsignificant level [13, 40, 41]. In this study, the positive association between moderate-to-severe OSA (AHI ≥15) and IAC scores was found only among nonobese participants, suggesting that obesity is a confounding factor between OSA and IAC. Additionally, the findings of this study suggest the importance of early screening for OSA, especially in nonobese individuals, for early intervention and prevention of cerebrovascular disease in these patients.

Strengths and Limitations

The main strengths of this study are the large sample of individuals, the detailed information on relevant confounders, as well as in-depth exploration of the relationship between OSA and IAC in different gender and obesity classifications, but some limitations should be addressed. A first limitation is that this was a cross-sectional study, and as such, we could not establish a cause-and-effect relationship between OSA and IAC scores. Second, we use a portable, although validated, sleep monitor, and several important sleep parameters were not captured. Third, in the current analysis, we did not explore the relationship between OSA and different patterns of IAC (intimal and medial calcification). However, we believe that follow-up studies are warranted as understanding the association of OSA with IAC patterns may help to explore the underlying mechanism of IAC formation. Finally, as the study population was limited to participants with suspected OSA, this might be a potential source for selection bias and thus may not be extrapolated to other populations.

Since the current research findings were acquired from one-center clinical study, further validations using a public database or other cohorts will make the findings more reliable. Based on these study findings, our research team will continue this study by exploring comparable public database or collaborating with another research institute for future validations. Moreover, performing a Mendelian randomization analysis to investigate the genomic relationship between OSA and IAC may provide an in-depth explanation of the underlying mechanism accounting for OSA-induced multisystem diseases. Future studies will be designed to analyze the genomic relationship between OSA and IAC.

Conclusion

These analyses found significant associations between severe OSA, with AHI ≥30 per h and IAC scores in a large-scale, hospital-based study, especially among women and no-obesity individuals.

Statement of Ethics

This study protocol was reviewed and approved by the Clinical Ethics Committees of the Second Affiliated Hospital of Guangzhou Medical University, approval number (2022-YJS-ks-03). Informed consent was waived because of the retrospective nature of the study, and the analysis used anonymous clinical data.

Conflict of Interest Statement

None reported.

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Author Contributions

Xuelong Li and Xiangyan Chen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Xuelong Li and Xiangyan Chen. Acquisition, analysis, or interpretation of data: Xuelong Li, Heng Du, Yangyang Cheng, Junru Chen, Yujing Zhang, and Jiewei Hua. Drafting of the manuscript and statistical analysis: Xuelong Li. Critical revision of the manuscript for important intellectual content: all the authors. Obtained funding: Xiangyan Chen. Administrative, technical, or material support: Xuelong Li and Xianliang Li. Supervision: Xiangyan Chen and Xianliang Li. For data sharing statement, see online supplement 2.

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