Relationship of obstructive sleep apnoea severity and subclinical systemic atherosclerosis

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In this large population-based study, obstructive sleep apnoea was associated with greater thoracic aorta calcification as early signs of cardiovascular disease, especially in patients with higher epicardial fat volume http://bit.ly/31v1jKV

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ABSTRACT Obstructive sleep apnoea (OSA) is a common form of sleep disordered breathing. Untreated OSA might accelerate atherosclerosis, potentially increasing the cardiovascular disease burden in patients. The present study aimed to evaluate the association between objectively measured OSA severity and the presence of subclinical systemic atherosclerosis using noninvasive measurements, including tomographic quantification of the calcium burden.

A total of 2157 participants of the Korean Genome and Epidemiology Study, who were free of structural heart disease and underwent both in-home polysomnography and chest computed tomography, were cross-sectionally analysed. Participants were divided into three groups based on the severity of OSA: no OSA (apnoea–hypopnoea index (AHI) <5 events·h^{-1}, n=1096), mild OSA (AHI 5–<15 events·h^{-1}, n=700) and moderate-to-severe OSA (AHI ⩾15 events·h^{-1}, n=361). Calcium deposits in the thoracic aorta and coronary arteries were measured by the Agatston score.

Participants with moderate-to-severe OSA were 1.6 times (95% CI 1.18–2.15 times; p=0.002) more likely to have ascending thoracic aorta calcification (⩾100 units) than those without OSA, after adjustment for cardiovascular risk factors. In addition, the association between moderate-to-severe OSA and ascending thoracic aorta calcification of subjects with higher epicardial fat volume was slightly stronger than that in patients without OSA and in the lowest epicardial fat volume tertile (OR 2.11, 95% CI 1.30–3.43).

Severity of OSA in the general population was independently associated with subclinical systemic atherosclerosis. These findings highlight the potential importance of severe OSA, especially in subjects with higher epicardial fat, as a possible predictive factor for systemic atherosclerosis and cardiovascular disease.

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Introduction

Obstructive sleep apnoea (OSA) is a common form of sleep disordered breathing characterised by repeated partial or complete obstruction of the upper airway, which leads to intermittent hypoxia, intrathoracic pressure changes and sleep fragmentation [1, 2]. The reported prevalence of OSA in the Asian population using sleep monitoring ranges from 9% to 89% (mild OSA from 30% to 89% and moderate-to-severe OSA from 9% to 51%). The overall prevalence of OSA in South Korea, ascertained using sleep questionnaires, was reported to be 15% [3, 4]. Although the measurement techniques and scoring criteria for OSA have changed over several decades, the awareness and knowledge of OSA among the general population is still poor. According to a population-based study, about one in five participants was aware of OSA and only one in 10 participants was able to define OSA correctly [5]. Unrecognised and untreated OSA was associated with increased healthcare utilisation and cost, as well as a higher comorbid diseases burden [6]. OSA can accelerate hypertension, diabetes, atherosclerosis, stroke and cardiovascular disease (CVD), potentially increasing cardiovascular mortality in patients with OSA [7–9]. Frequently occurring and coexisting cardio-metabolic disorders make it difficult to assess the independent effect of OSA on the progression of atherosclerosis as well as CVD [10].

Scoring the amount of calcium in the aorta and coronary arteries using cardiac and chest computed tomography (CT) provides a noninvasive measure of the subclinical atherosclerotic burden. Increased calcification in both the aorta and coronary arteries has been established as a distinct marker of underlying atherosclerosis in the vascular beds, and has been identified to provide further prognostic information on CVD [11–13]. Moreover, accumulating evidence has linked sleep disturbances to increased coronary artery calcification (CAC) and inflammation may represent an important factor with respect to OSA-induced atherosclerotic calcification; however, the results of these studies have been inconsistent [13–17]. Some results have revealed the association to be nonsignificant after adjustment for cardiovascular risk factors, such as body mass index (BMI) [16]. These inconsistencies illustrate the complexity of the interaction between sleep disordered breathing and atherosclerotic calcification, as well as the multifactorial involvement of increased cardiovascular risk associated with OSA.

In addition, carotid intima–media thickness (cIMT) and pulse wave velocity (PWV) by noninvasive measurements are early indicators of subclinical atherosclerosis that predict future CVD events [18]. In systematic and meta-analysis studies, patients with OSA had significantly higher cIMT and PWVs, suggestive of an atherosclerotic process, but there was significant heterogeneity [19]. In other words, various cardiovascular risk factors have been associated with an increase in cIMT and PWV, and OSA is one such potential risk factor. In addition, increased atherosclerosis and vascular stiffness may occur with increased severity of OSA in asymptomatic CVD.

The present study aimed to evaluate the association between objectively measured OSA severity and the presence of subclinical systemic atherosclerosis using noninvasive measurements, including tomographic quantification of the calcium burden in the aorta and coronary arteries in healthy individuals without structural heart disease. Furthermore, we examined whether epicardial fat volume (EFV) as an unambiguous cardiovascular risk factor has a moderating effect on the relationship between OSA severity and the presence of subclinical systemic atherosclerosis.

Material and methods

Study design and population

This cross-sectional study was performed from a population-based cohort comprised of Korean males and females aged 39–70 years. All subjects were participants between 2001 and 2002 in the Korean Genome and Epidemiology Study (KoGES), which is an ongoing prospective investigation. Detailed information on participant recruitment is available [20, 21]. Briefly, a total of 5012 participants from Ansan, Republic of Korea, were examined at baseline from 2001 to 2002. Cohort members completed a comprehensive health examination and questionnaire-based interview, and biospecimens for assays were collected by health professionals. The health examination was comprised of anthropometric and clinical evaluations, including chest radiography. The questionnaire covered demographic characteristics, lifestyle and medical history. Follow-up examinations were performed biennially during a scheduled site visit. The eighth examination was performed between March 2015 and December 2016, and was attended by 3083 individuals. Of these participants, 2378 underwent overnight in-home polysomnography (PSG) and chest CT for the measurement of the calcification of the thoracic aorta and coronary arteries and EFV measurement. From this sample, we further excluded participants with prevalent myocardial infarction, angina pectoris, congenital heart failure, arrhythmia or stroke (n=221). The final data were analysed from 2157 individuals (figure 1).

Written informed consent was obtained from all participants at every site visit. The study protocol was approved by the Institutional Ethics Committee of Korea University Ansan Hospital (Ansan).

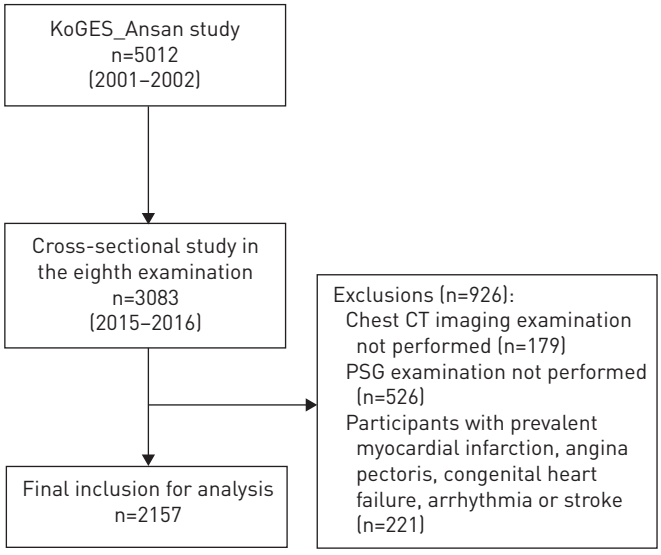

FIGURE 1 Flow diagram of participants in the Korean Genome and Epidemiology Study (KoGES)_Ansan study, 2001–2016. CT: computed tomography; PSG: polysomnography.

Polysomnography

Overnight in-home PSG was performed using a portable monitoring device (Embletta X-100; Embla Systems, Broomfield, CO, USA) with channels for electroencephalography, ECG, a pressure transducer airflow sensor, a chest and abdominal respiratory movement sensor, and a snore sensor. A trained technician connected the device to the patient at bedtime, data were collected the morning after the unattended overnight recording and the PSG results were manually scored according to standard criteria [22]. An oxygen desaturation event was detected when the oxygen saturation dropped by at least 4%. All saturations values <50% were excluded as artefact values and not counted as part of a desaturation event. An apnoea event was detected if both of the following criteria were met: 1) there was a drop in the peak signal excursion by ⩾90% of the pre-event baseline (reference amplitude) and 2) the duration of the ⩾90% drop in sensor signal was ⩾10 s. In addition, a hypopnoea event was detected if all of the following criteria were met: 1) the peak signal excursions dropped by ⩾30% of the reference amplitude, 2) the duration of the ⩾30% drop in signal excursions was ⩾10 s and 3) there was ⩾3% oxygen desaturation from the reference amplitude or the event was associated with an arousal. The reference amplitude was calculated as the mean value of the peak amplitudes in the period of 100 s preceding the event. The apnoea–hypopnoea index (AHI) was calculated by averaging the total number of obstructive apnoea and hypopnoea events per hour of sleep, and OSA severity was defined according to different levels of AHI: no OSA (AHI <5 events·h^{-1}), mild OSA (AHI 5–<15 events·h^{-1}) and moderate-to-severe OSA (AHI ⩾15 events·h^{-1}).

Chest CT imaging protocol and measurements

Details on the procedures for chest CT data acquisition, scanner quality assurance and scan reading have been previously described [23]. Briefly, well-trained technicians performed chest CT scans using a 64-multidetector CT scanner (Brilliance 64; Philips Healthcare, Cleveland, OH, USA) following a standardised protocol, with each participant in the supine position during end-inspiratory and end-expiratory breath-hold. Scanning parameters were held constant at the 64×0.625 mm detector configuration, 120 kV (peak), 100 mAs and a section thickness of 0.625 mm without intravenous contrast material.

The presence of aortic calcification was defined as the presence of at least one detectable lesion. We quantified calcifications in the walls of the ascending and descending thoracic aorta from the aortic root (above the left main coronary artery) to the level of the diaphragmatic crura (below both the ventricles). All calcification scores were calculated using the Agatston scoring method [24].

EFV was measured three-dimensionally in all patients using noncontrast chest CT images [24, 25]. Epicardial fat was defined as fat enclosed in the visceral pericardium. Segmentation of the overall volume was automatically interpolated using manually defined tracings and EFV was subsequently quantified by calculating the total volume of the tissue in which CT density ranged from −500 to 0 HU within the pericardial cavity.

Quantitative analysis of aortic calcification and EFV was performed using Aquarius iNtuition Edition version 4.4.11 (TeraRecon, Foster City, CA, USA), which is an automated lung image analysis tool.

Common cIMT and PWV measurements

Measurements of cIMT on the right and left carotid arteries were performed using B-mode ultrasonography (Titan; Sonosite, Tokyo, Japan) with a 7.5 MHz linear array transducer. For IMT measurements, images of the distal common carotid arteries were obtained at both the far and near walls, ~1 cm proximal to the bulb. In each segment, the mean values of the common carotid arteries IMT (CCA-IMT) were calculated as the average of the left and right CCA-IMT scores obtained from the near and far walls using semiautomated software (M'ATH SR version 2.0; Metris, Argenteuil, France). Two technicians were trained with an authorised protocol and certified, and the intraclass correlation coefficient values obtained from them was >0.90 for each segment (range 0.910–0.941) [26].

The brachial–ankle PWV (baPWV) was measured in the supine position using an automatic volume-plethysmographic device (VP2000; Colin, Komaki, Japan). The PWV was defined as the distance of two sites over the pulse transit time. The time interval between the brachium and the ankle was defined as the time interval between the wave front of the brachial waveform and that of the ankle waveform. The distance between sampling points of the baPWV was calculated automatically according to the heights of the subjects [27].

Other variables

Demographic data, smoking status, amount of alcohol consumed, physical activity and medical conditions were obtained *via* a questionnaire. Physical activity was assessed using a scale consisting of five categories for activity intensity as measured by hours spent in a typical day per intensity level. The total metabolic equivalent (MET·week^{-1}) score was calculated by multiplying the hours spent at a particular activity intensity by the MET value. BMI was calculated as weight (kg) divided by height squared (m^2). Blood samples were collected after a fasting period of at least 8 h. Fasting glucose, haemoglobin A1c, total cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol and high-sensitivity C-reactive protein (hsCRP) levels were measured using standardised enzymatic methods in a commercial laboratory (Seoul Clinical Laboratories, Seoul, Republic of Korea). Low-density lipoprotein (LDL)-cholesterol levels were estimated using the Friedewald formula. Hypertension was defined as a systolic blood pressure of ⩾140 mmHg, a diastolic blood pressure of ⩾90 mmHg or the current use of antihypertensive medications. Type 2 diabetes was defined as a fasting blood glucose level of ⩾126 mg·dL^{-1} or the use of insulin or oral hypoglycaemic medications.

Statistical analysis

The general characteristics of participants are presented as mean with standard deviation and proportions, stratified by OSA severity (AHI <5, 5–<15 and ⩾15 events·h^{-1}) using the Chi-squared test or one-way ANOVA for categorical and continuous variables, respectively. Because thoracic aorta calcification (TAC) and CAC scores had a highly positively skewed distribution, we used log-transformed values (log (raw score+1)) to deal with individuals who had raw scores of zero. The associations between the subclinical systemic atherosclerosis parameters and severity of OSA were determined using one-way ANCOVA and the *post hoc* Scheffe test. In the intervening time, subjects were classified into two groups according to the presence or absence of TAC or CAC using each raw Agatston score: the presence of ascending TAC (aTAC score ⩾100 units), descending TAC (dTAC score ⩾100 units), overall TAC (TAC score ⩾400 units) and CAC (CAC score >0 units). Multivariate logistic regression analysis was performed to determine the effects of subclinical systemic atherosclerosis. Model 1 was unadjusted, whereas model 2 was adjusted for age, sex and BMI. Additionally, model 3 was also adjusted for hypertension, type 2 diabetes, HDL-cholesterol, LDL-cholesterol and pack-years of smoking. Tests for moderate effects were examined to assess whether the associations between OSA and subclinical systemic atherosclerosis varied across EFV tertiles. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Descriptive analysis

A total of 2157 participants (mean age 59.96±6.67 years; 48.73% male) were examined. Of all the participants, 50.81% had no OSA (AHI <5 events·h^{-1}), 32.45% had mild OSA (AHI 5–<15 events·h^{-1}) and 16.74% had moderate-to-severe OSA (AHI ⩾15 events·h^{-1}). Participants with moderate-to-severe OSA were slightly older (62.08±7.63 *versus* 58.76±5.96 years; p<0.001), were more often male (68.14% *versus* 41.61%; p<0.001), had a higher EFV (285.24±69.69 *versus* 234.13±59.97 cm^3; p<0.001), higher prevalence of hypertension (62.60% *versus* 34.12%; p<0.001) and type 2 diabetes (43.21% *versus* 25.64%; p<0.001), and had lower levels of HDL-cholesterol (43.09±10.82 *versus* 48.20±12.06 mg·dL^{-1}; p<0.001) than individuals without OSA. Interestingly, hsCRP levels and physical activity were not different among the OSA severities (table 1).

TABLE 1 Comparison of clinical characteristics according to the severity of obstructive sleep apnoea (OSA)

	No OSA (AHI <5 events·h^{-1})	Mild OSA (AHI 5– <15 events·h^{-1})	Moderate-to-severe OSA (AHI ⩾15 events·h^{-1})	p-value#	p-value¶
Subjects	1096 (50.8)	700 (32.5)	361 (16.7)		
Age years	58.8±6.0	60.8±6.8	62.1±7.6	<0.001	
Male	456 (41.6)	349 (49.9)	246 (68.1)	<0.001	
BMI kg·m^{-2}	23.8±2.6	25.2±2.9	26.1±3.3	<0.001	<0.001+
Waist circumference cm	80.6±7.5	85.2±8.2	88.6±8.6	<0.001	<0.001+
EFV cm^3	234.1±60.0	260.3±66.8	285.2±69.7	<0.001	<0.001+
Systolic blood pressure mmHg	113.4±14.3	116.0±13.4	118.5±13.1	<0.001	0.002+
Diastolic blood pressure mmHg	73.4±8.9	74.6±9.0	76.7±9.2	<0.001	<0.001+
Fasting glucose mg·dL^{-1}	94.9±19.4	99.2±22.7	102.7±22.3	<0.001	<0.001+
HbA1c %	5.7±0.7	5.9±0.9	6.0±0.8	<0.001	<0.001+
Total cholesterol mg·dL^{-1}	197.9±36.3	192.5±35.9	189.6±35.5	<0.001	0.22
Triglyceride mg·dL^{-1}	129.6±80.4	140.3±94.0	154.7±91.2	<0.001	<0.001+
HDL-cholesterol mg·dL^{-1}	48.2±12.1	46.4±11.2	43.1±10.8	<0.001	<0.001+
LDL-cholesterol mg·dL^{-1}	124.5±32.7	119.2±31.6	116.6±32.3	<0.001	0.06
hsCRP mg·dL^{-1}	1.3±2.3	1.3±2.5	1.5±3.7	0.26	0.33
Pack-years of smoking	7.9±15.3	9.4±16.0	13.7±19.2	<0.001	0.64
Alcohol consumption g·day^{-1}	7.4±18.9	8.9±20.0	11.1±22.8	0.01	0.70
Physical activity MET·week^{-1}	798.2±988.7	809.1±940.4	896.6±1145.5	0.26	0.79
Hypertension	374 (34.1)	353 (50.4)	226 (62.6)	<0.001	<0.001
Type 2 diabetes	281 (25.6)	227 (32.4)	156 (43.2)	<0.001	<0.001
Polysomnographic recordings					
AHI events·h^{-1} TST	2.1±1.4	8.7±2.7	26.1±12.1	<0.001	<0.001+
Supine AHI events·h^{-1} TST	4.3±5.5	17.5±12.0	41.8±18.9	<0.001	<0.001+
Nonsupine AHI events·h^{-1} TST	0.8±1.2	2.8±2.9	11.2±13.5	<0.001	<0.001+
TST min	371.4±80.0	365.9±76.7	366.2±79.8	0.28	0.70
Awakening index >30 s events·h^{-1}	4.7±3.6	5.3±3.3	7.0±4.9	<0.001	<0.001+
Mean S_{aO_2} %	95.9±1.1	95.2±1.2	94.4±1.5	<0.001	<0.001+
Lowest S_{aO_2} %	89.6±5.3	85.1±4.7	80.4±6.7	<0.001	<0.001+
Oxygen desaturation index events·h^{-1} TST	1.9±0.3	7.9±2.9	24.0±11.6	<0.001	<0.001+
S_{aO_2} <90% min	0.5±2.7	2.6±4.6	16.2±26.0	<0.001	<0.001+
S_{aO_2} <90% % TST	0.2±0.9	0.8±3.2	4.7±7.9	<0.001	<0.001+

Data are presented as n (%) or mean±SD, unless otherwise stated. AHI: apnoea–hypopnoea index; BMI: body mass index; EFV: epicardial fat volume; HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; MET: metabolic equivalent; TST: total sleep time; S_{aO_2}: arterial oxygen saturation. #: p-values for unadjusted model; ¶: p-values for multivariate models including age and sex where applicable; +: p<0.05 among all comparisons by the *post hoc* Scheffe test.

Comparisons of polysomnographic parameters and OSA severity are reported in table 1. Supine AHI (4.26±5.49 *versus* 41.75±18.87 events·h^{-1}), nonsupine AHI (0.80±1.16 *versus* 11.24±13.50 events·h^{-1}) and oxygen desaturation index (1.89±0.32 *versus* 24.04±11.62 events·h^{-1}) as well as total AHI (2.05±1.40 *versus* 26.12±12.11 events·h^{-1}) were higher in the moderate-to-severe OSA group than in the no OSA group (all adjusted p<0.001). Total sleep time was not different according to OSA severity; however, the awakening index of >30 s·h^{-1} was greater in the moderate-to-severe OSA group than in the no OSA group (4.67±3.63 *versus* 6.96±4.85 events·h^{-1}; adjusted p<0.001).

Severity of OSA and subclinical systemic atherosclerosis

Comparisons of measurements for subclinical systemic atherosclerosis parameters among OSA severities are reported in table 2. After adjusting for cardiovascular risk factors, baPWV and ankle–brachial index (ABI) on the right ankle were increased in the moderate-to-severe OSA patients compared with individuals without OSA (baPWV: 1437.76±234.70 *versus* 1569.14±321.18; ABI: 1.167±0.076 *versus* 1.182±0.087; all p<0.05).

The median aTAC score was significantly higher in mild OSA (3.2 units) and moderate-to-severe OSA individuals (50.0 units) than in those without OSA (0.0 units) (p_{trend}=0.02). The associations of dTAC and TAC with OSA severity were similar to the trend of aTAC (p_{trend}=0.008 and 0.006, respectively) (table 2 and figure 2). Moderate-to-severe OSA was associated with aTAC (⩾100 units) in the univariate logistic regression (OR 2.70, 95% CI 2.10–3.47; p<0.001). In multivariate analyses, moderate-to-severe OSA remained independently associated with aTAC after adjusting for age, sex, BMI, hypertension, type 2

TABLE 2 Associations with subclinical systemic atherosclerosis parameters and obstructive sleep apnoea (OSA) severity

	No OSA (AHI <5 events·h^{-1})	Mild OSA (AHI 5– <15 events·h^{-1})	Moderate-to-severe OSA (AHI ⩾15 events·h^{-1})	p-value[#]
Subjects	1096 (50.81)	700 (32.45)	361 (16.74)	
Common carotid artery IMT mm				
Mean far wall IMT	0.730±0.083	0.741±0.082	0.762±0.085	0.24
Mean near wall IMT	0.726±0.082	0.745±0.077	0.755±0.085	0.75
Mean near and far wall IMT	0.729±0.072	0.743±0.069	0.759±0.074	0.86
PWV				
Brachial–ankle PWV, right cm·s^{-1}	1437.76±234.70	1495.38±247.07	1569.14±321.18	0.05[¶,+,§]
Brachial–ankle PWV, left cm·s^{-1}	1433.40±233.71	1487.78±246.73	1555.17±288.73	0.14
Ankle–brachial index, right	1.167±0.076	1.180±0.066	1.182±0.087	0.003[¶,+]
Ankle–brachial index, left	1.156±0.071	1.169±0.064	1.167±0.072	0.007[¶]
Agatston score				
Ascending TAC	0.0 (0.0–5782.8)	3.2 (0.0–4955.9)	50.0 (0.0–20 749.0)	0.02[¶,+,§]
Descending TAC	11.2 (0.0–26 255.3)	50.9 (0.0–21 430.5)	108.0 (0.0–55 353.6)	0.008[¶,+,§]
TAC	37.9 (0.0–27 204.0)	123.6 (0.0–22 167.0)	265.5 (0.0–59 565.7)	0.006[¶,+,§]
CAC	0.0 (0.0–3039.4)	0.0 (0.0–1583.4)	0.0 (0.0–1808.6)	0.29

Data are presented as n (%), mean±SD or median (range), unless otherwise stated. AHI: apnoea–hypopnoea index; IMT: intima–media thickness; PWV: pulse wave velocity; TAC: thoracic aorta calcification; CAC: coronary artery calcification. [#]: p-values for one-way ANCOVA including age, sex, body mass index, hypertension, type 2 diabetes, high-density lipoprotein cholesterol, how-density lipoprotein cholesterol and pack-years of smoking; [¶]: p<0.05 when comparing no OSA to mild OSA by the *post hoc* Scheffe test; [+]: p<0.05 when comparing no OSA to moderate-to-severe OSA by the *post hoc* Scheffe test; [§]: p<0.05 when comparing mild OSA to moderate-to-severe OSA by the *post hoc* Scheffe test.

diabetes, HDL-cholesterol, LDL-cholesterol and pack-years of smoking (OR 1.59, 95% CI 1.18–2.15; p=0.002) (table 3). Both dTAC (⩾100 units) and TAC (⩾400 units) also had a positive correlation with moderate-to-severe OSA (OR 1.52, 95% CI 1.12–2.07; p=0.007 and OR 1.51, 95% CI 1.10–2.07; p=0.01, respectively). Based on unadjusted logistic regression, moderate-to-severe OSA was associated with CAC (>0 units) (OR 1.96, 95% CI 1.51–2.53; p<0.001), but the relationship was not significant after adjusting for cardiovascular risk factors (OR 1.05, 95% CI 0.78–1.42; p=0.75).

Joint effects of OSA severity and EFV in subclinical systemic atherosclerosis

As shown in table 4, participants with moderate-to-severe OSA were 1.14 times (95% CI 0.76–1.72 times) more likely to have aTAC (⩾100 units) relative to participants without OSA among participants in the

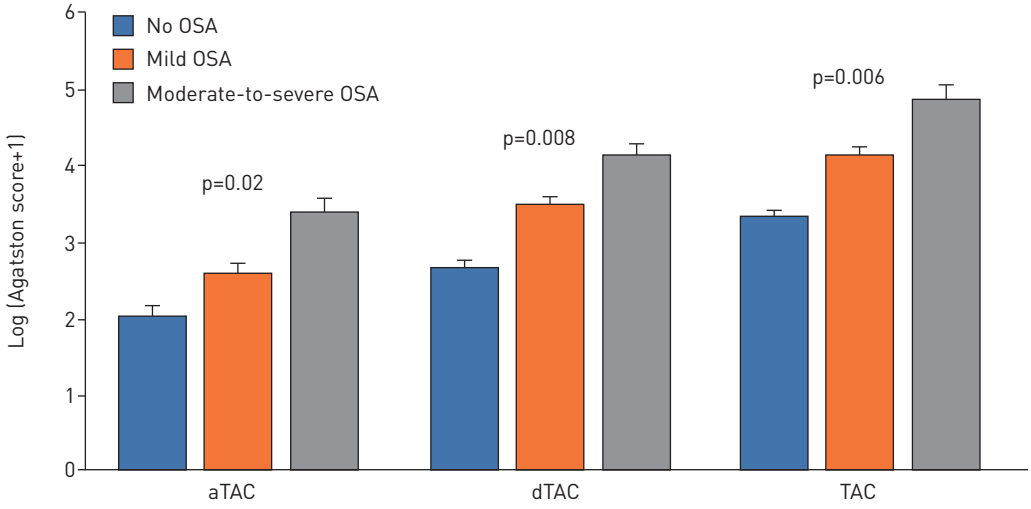

FIGURE 2 Severity of obstructive sleep apnoea (OSA) and thoracic aorta calcifications (TACs): ascending TAC (aTAC), descending TAC (dTAC) and TAC. TACs, which are useful predictors of subclinical systemic atherosclerosis, increased according to OSA severity (all adjusted p<0.001 using ANCOVA). All p-values are adjusted by age, sex, body mass index, hypertension, type 2 diabetes, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and pack-years of smoking. Error bars represent standard error.

TABLE 3 Multivariate logistic regression analyses of the relationship between obstructive sleep apnoea (OSA) severity and the presence of thoracic aorta calcification (TAC) and coronary artery calcification (CAC)

	No OSA (AHI <5 events·h^{-1})	Mild OSA (AHI 5–<15 events·h^{-1})		Moderate-to-severe OSA (AHI ⩾15 events·h^{-1})		p_{trend}
		OR (95% CI)	p-value	OR (95% CI)	p-value	
Subjects	1096 (50.81)	700 (32.45)		361 (16.74)		
aTAC (⩾100 units)						
Subjects	260 (23.72)	229 (32.71)		165 (45.71)		
Model 1	Reference	1.57 (1.27–1.93)	<0.001	2.70 (2.10–3.47)	<0.001	<0.001
Model 2	Reference	1.20 (0.95–1.51)	0.13	1.74 (1.31–2.33)	<0.001	<0.001
Model 3	Reference	1.14 (0.90–1.46)	0.27	1.59 (1.18–2.15)	0.002	0.003
dTAC (⩾100 units)						
Subjects	308 (28.10)	291 (41.57)		178 (49.31)		
Model 1	Reference	1.81 (1.48–2.21)	<0.001	2.54 (1.98–3.25)	<0.001	<0.001
Model 2	Reference	1.40 (1.11–1.76)	0.004	1.67 (1.24–2.25)	<0.001	<0.001
Model 3	Reference	1.35 (1.07–1.71)	0.01	1.52 (1.12–2.07)	0.007	0.003
TAC (⩾400 units)						
Subjects	235 (21.44)	231 (33.00)		157 (43.49)		
Model 1	Reference	1.81 (1.46–2.23)	<0.001	2.82 (2.19–3.63)	<0.001	<0.001
Model 2	Reference	1.31 (1.03–1.67)	0.03	1.61 (1.19–2.19)	0.002	0.001
Model 3	Reference	1.25 (0.97–1.61)	0.09	1.51 (1.10–2.07)	0.01	0.008
CAC (>0 units)						
Subjects	248 (22.63)	181 (25.86)		131 (36.29)		
Model 1	Reference	1.19 (0.96–1.49)	0.12	1.96 (1.51–2.53)	<0.001	<0.001
Model 2	Reference	0.91 (0.72–1.16)	0.44	1.16 (0.86–1.55)	0.33	0.51
Model 3	Reference	0.84 (0.66–1.08)	0.18	1.05 (0.78–1.42)	0.75	0.98

Data for numbers of subjects are presented as n (%). AHI: apnoea–hypopnoea index; aTAC: ascending TAC; dTAC: descending TAC. Model 1: unadjusted. Model 2: adjusted for age, sex and body mass index. Model 3: adjusted model 2, hypertension, type 2 diabetes, high-density lipoprotein cholesterol, how-density lipoprotein cholesterol and pack-years of smoking.

TABLE 4 Multivariate logistic regression analysis of the presence of thoracic aorta calcification (TAC) and coronary artery calcification (CAC) for moderation effect of obstructive sleep apnoea (OSA) severity and epicardial fat volume (EFV)

	No OSA (AHI <5 events·h^{-1})		Mild OSA (AHI 5–<15 events·h^{-1})		Moderate-to-severe OSA (AHI ⩾15 events·h^{-1})	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Subjects	1096 (50.81)		700 (32.45)		361 (16.74)	
aTAC (⩾100 units)						
Lower EFV tertile (T1)	Reference		1.04 (0.72–1.51)	0.83	1.14 (0.76–1.72)	0.54
Middle EFV tertile (T2)	0.87 (0.55–1.35)	0.53	1.35 (0.89–2.04)	0.16	1.46 (0.96–2.23)	0.08
Upper EFV tertile (T3)	1.01 (0.54–1.92)	0.97	1.86 (1.14–3.05)	0.01	2.11 (1.30–3.43)	0.003
dTAC (⩾100 units)						
Lower EFV tertile (T1)	Reference		0.75 (0.52–1.08)	0.12	1.08 (0.73–1.62)	0.70
Middle EFV tertile (T2)	0.98 (0.64–1.50)	0.93	1.59 (1.06–2.37)	0.02	1.22 (0.80–1.85)	0.36
Upper EFV tertile (T3)	1.37 (0.73–2.58)	0.33	1.51 (0.92–2.49)	0.11	1.38 (0.84–2.26)	0.21
TAC (⩾400 units)						
Lower EFV tertile (T1)	Reference		0.63 (0.42–0.94)	0.02	0.89 (0.58–1.38)	0.60
Middle EFV tertile (T2)	0.76 (0.48–1.22)	0.43	1.19 (0.77–1.83)	0.43	1.13 (0.73–1.75)	0.60
Upper EFV tertile (T3)	0.99 (0.51–1.92)	0.97	1.41 (0.84–2.36)	0.20	1.29 (0.77–2.14)	0.33
CAC (>0 units)						
Lower EFV tertile (T1)	Reference		1.27 (0.87–1.84)	0.21	1.35 (0.89–2.04)	0.16
Middle EFV tertile (T2)	0.83 (0.52–1.31)	0.42	0.98 (0.63–1.53)	0.94	1.19 (0.77–1.83)	0.43
Upper EFV tertile (T3)	1.62 (0.88–2.98)	0.12	1.17 (0.71–1.95)	0.54	1.29 (0.79–2.10)	0.32

Data for numbers of subjects are presented as n (%). AHI: apnoea–hypopnoea index; aTAC: ascending TAC; dTAC: descending TAC. The logistic regression analysis was adjusted for age, sex, body mass index, hypertension, type 2 diabetes, high-density lipoprotein cholesterol, how-density lipoprotein cholesterol and pack-years of smoking.

lowest EFV tertile (T1). However, participants with the highest EFV tertile (T3) were 1.01 times (95% CI 0.54–1.92 times) more likely to have aTAC than participants with the lowest EFV tertile (T1) within those without OSA. The association between moderate-to-severe OSA and aTAC among participants in the highest EFV tertile (T3) was slightly stronger than in those without OSA and in the lowest EFV tertile (T1) after adjustment for cardiovascular risk factors (OR 2.11, 95% CI 1.30–3.43; p=0.003). In addition, there was a moderate effect by EFV tertiles ($p_{interaction}$<0.001) (figure 3).

Discussion

The principal finding of this study was that OSA severity, especially moderate-to-severe OSA, is independently associated with the presence of TAC, a useful predictor of subclinical systemic atherosclerosis in the general population without structural heart disease. In addition, we found an effect modification of EFV between OSA severity and TAC after adjustment for cardiovascular risk factors.

During non-rapid eye movement sleep, both the metabolic rate and the sympathetic nervous system activity normally decrease. However, sleep disordered breathing, such as OSA, interrupts this stationary phase by triggering a cascade of acute haemodynamic, inflammatory and metabolic effects, with chronic after-effects capable of initiating or exacerbating CVD [28]. Thus, repeated upper airway collapse and apnoeic spells result in arterial oxygen desaturation and arousal during sleep, leading to CVD such as blood pressure elevation and endothelial dysfunction [29]. The pathogenesis appears likely to be a multifactorial process involving a diverse range of mechanisms, including sympathetic nervous system overactivity, selective activation of inflammatory pathways, endothelial dysfunction and metabolic dysregulation [30], leading to increased arterial stiffness, arterial hypertension and the development of CVD. Several studies have reported the association between OSA and a higher incidence of CVD due to subclinical myocardial infarction or fatal CVD [15, 31]. In addition, endothelial dysfunction has been shown to develop in patients with OSA [32]. These trends have also been demonstrated in our study as the moderate-to-severe OSA group exhibited higher cardiovascular risk factors and a higher prevalence of hypertension and diabetes than the no OSA group.

Findings from studies determining the impact of OSA on vascular disease including the aorta have discussed several pathophysiological mechanisms, such as intrathoracic pressure swings leading to shear stress on artery walls, intermittent hypoxia leading to oxidative stress and sympathetic stimulation, and

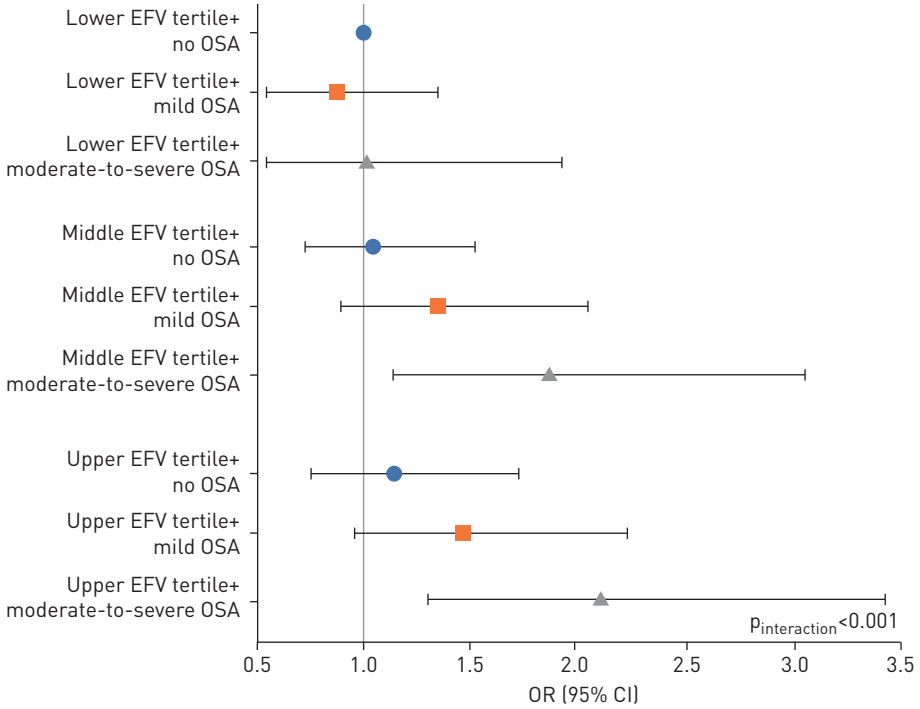

FIGURE 3 Joint effects of obstructive sleep apnoea (OSA) severity and epicardial fat volume (EFV) tertiles in the presence of ascending thoracic aorta calcification (aTAC ⩾100 units). Joint effects of OSA severity and EFV tertiles showed higher aTAC; the presence of aTAC was significantly higher in the upper EFV tertile (T3) group among participants with moderate-to-severe OSA than in the lower EFV tertile (T1) group among participants without OSA and this effect was dose-dependent on OSA severity.

arousal-induced sympathetic activation with subsequent repetitive blood pressure elevations [2, 33]. The association between OSA and atherosclerotic diseases according to vascular calcification is highly suggestive, based on several epidemiological studies [13–17, 34, 35]. One study showed that subjects with severe OSA were more likely to have coronary atherosclerotic calcification (defined as CAC score >0 Agatston units) than those without OSA after adjusting for traditional cardiovascular risk factors [13], while less data are currently available regarding the association between OSA and aorta calcification. Recent evidence has indicated that OSA is associated with a greater extent of abdominal aortic calcification compared with no OSA [36].

Our study has demonstrated a significant relationship between moderate-to-severe OSA and TAC, but not with CAC. One possibility is that the impact of OSA on pathogenic pathways of developing atherosclerosis differs between CAC and TAC. TAC may represent systemic atherosclerosis burden especially better than CAC [37]. CAC is completely associated with atherosclerosis; however, TAC involves two pathophysiological processes: intimal, which is atherosclerotic, and medial, which contributes to increased aortic stiffness [37]. The potential impact of OSA on cardiovascular burden and aortic disease is likely to be related in large part to its association with elevated blood pressure. Previous cohort studies have consistently demonstrated that >50% of subjects with OSA have hypertension [33], which has been revealed in our study as well (table 1). Hypertension more strongly influenced the aorta than the coronary artery [38] and aortic stiffness closely associated with aortic calcification is directly related to elevated systolic blood pressure [39]. It is generally accepted that hypertension can cause thoracic aortic dilation [40] and it is the main risk factor for aortic dissection [41], although the exact pathophysiology remains unclear. Unfortunately, although chest CT cannot differentiate between intimal and medial calcification, the contribution of medial calcification in TAC may be more significant for systemic atherosclerosis. In this study, the association with OSA severity and calcifications differed between the hypertensive and normotensive subgroups. In the normotensive group, OSA severity was not associated with any calcification scores. However, in the hypertensive group, OSA severity was associated with TACs up to 2.21 times higher than without OSA (supplementary table E1). It is therefore thought that OSA may act through other complex pathological mechanisms to elicit vascular damage.

Another possibility is that the thoracic aorta might be more vulnerable than the coronary arteries due to intrathoracic pressure swings related to OSA. The repetitive forced inspiration against the obstructed upper airway generates negative changes in intrathoracic pressure [33]. These forces lead to the vascular pressure stretching the aortic walls where blood pressure surges are highest and cause pathological shear stress. It is known that systolic blood pressure hastens the fragmentation of fibrin and collagen deposition with secondary stiffening of the aortic wall. Additional physical dilation or shear stress itself might be another important factor for developing atherosclerosis [2]. There is also the sequential development during life as aortic atherosclerosis is in general encountered earlier than coronary and carotid atherosclerosis [42]. In the present study, the presence of any TAC (including aTAC and dTAC) was already observed in individuals without CAC (supplementary figure E2). These results support the notion that OSA severity is more strongly related to TAC than CAC, especially in the general population without structural heart disease.

Obesity has been hypothesised to affect breathing by causing alterations in the upper airway structure or function, disturbances in the relationship between respiratory drive and load compensation, and exacerbations of sleep disordered breathing *via* obesity-related reductions in functional residual capacity and increased whole-body oxygen demand. EFV is well correlated with the presence of abdominal visceral adipose tissue [43]. In the present study, there was a positive correlation between EFV and body composition, including BMI and waist circumference (BMI: r=0.60, 95% CI 0.57–0.62; waist circumference: r=0.67, 95% CI 0.65–0.69) (supplementary figure E1). Epicardial adipose tissue has been associated with the presence and severity of coronary artery disease in numerous studies [23, 44]. Furthermore, several case–control studies have investigated the relationship between epicardial adipose tissue and the presence and severity of OSA [45, 46], particularly in obese patients [1, 47]. Vascular calcification plays an important role in atherosclerosis, as well as in lipid accumulation and inflammation. In our previous preliminary study, both OSA and obesity were strongly associated with the presence and severity of a subclinical atherosclerotic burden, but the association between OSA and CAC became insignificant after further adjustment for BMI [16]. However, in this study, the presence of aTAC was higher in participants with moderate-to-severe OSA than in those without OSA, according to EFV tertiles. Moreover, the association between OSA and TAC was also significant after adjusting for EFV as well as BMI. Meanwhile, the presence of TAC was lower in mild OSA individuals (AHI 5–<15 events·h^{-1}) than in those without OSA among the lower EFV tertile group. The protective effects of low-frequency exposures to intermittent hypoxia can be explained by the activation of homeostatic or adaptive responses elicited by the intermittent hypoxia stimulus as preconditioning effects before the chronic pathophysiological process [48].

The strengths of this study are the inclusion of large general population-based samples, and the use of both objectively measured OSA severity by PSG and tomographic quantification of the calcium burden by noninvasive measurements. However, some limitations need to be considered when interpreting the results of our study. We used a cross-sectional study design; thus, a causal relationship needs to be determined in future studies.

In conclusion, our results support the finding that severity of OSA in general participants without structural heart disease is independently associated with subclinical systemic atherosclerosis. Multiple comorbid cardio-metabolic disorders of patients with OSA, especially in subjects with more epicardial fat, must be taken into consideration when investigating OSA-associated cardiovascular risk and systemic atherosclerosis. The challenges for future perspectives are in the development of specific preventive strategies targeting the pathways of cardiovascular calcification induced by severe intermittent hypoxia.

Conflict of interest: None declared.

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