https://doi.org/10.5664/jcsm.9356

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Sleep apnea, coronary artery calcium density, and cardiovascular events: results from the Multi-Ethnic Study of Atherosclerosis

Seth B. Newman, MD[1]; Vaishnavi Kundel, MD[2]; Mika Matsuzaki, PhD[3]; Michelle Reid, MPH[4]; Jorge R. Kizer, MD[5]; Robert C. Kaplan, PhD[1]; Zahi A. Fayad, PhD[2]; Venkatesh Mani, PhD[2]; Steven Shea, MD, MS[6]; Matthew Allison, MD, MPH[7]; Michael H. Criqui, MD[7]; Pamela L. Lutsey, PhD, MPH[8]; Robyn L. McClelland, PhD[3]; Susan Redline, MD, MPH[4]; Neomi A. Shah, MD, MPH, MS[2]

[1]Montefiore Medical Center, Bronx, New York; [2]Icahn School of Medicine at Mount Sinai, New York, New York; [3]University of Washington, School of Public Health, Seattle, Washington; [4]Brigham and Women's Hospital, Boston, Massachusetts; [5]San Francisco Veterans Affairs Health Care System and University of California San Francisco, San Francisco, California; [6]Vagelos College of Physicians and Surgeons, Columbia University, New York, New York; [7]University of California, San Diego, La Jolla, California; [8]University of Minnesota, Minneapolis, Minnesota

Study Objectives: Evaluate the association between obstructive sleep apnea (OSA), coronary artery calcium (CAC) density, and cardiovascular events in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods: We analyzed 1,041 participants with nonzero CAC scores who had polysomnography and CAC density data from the fifth examination of the Multi-Ethnic Study of Atherosclerosis. OSA was defined as apnea-hypopnea index ≥ 15 events/h. Multivariable linear regression models were used to evaluate the independent association between OSA and CAC density. Additionally, we evaluated the impact of OSA on associations of CAC measures with incident cardiovascular disease events by testing for interaction in Cox proportional hazard regression models.

Results: Our analytical sample was 45% female with a mean age of 70.6 +/− 9 years. Of this sample, 36.7% (n = 383/1041) had OSA (apnea-hypopnea index ≥ 15 events/h). OSA was inversely and weakly associated with CAC density (β = –0.09; 95% CI, –0.17 to –0.02; *P* = .014) and remained significantly associated after controlling for traditional cardiovascular risk factors (β = –0.08; 95% CI, –0.16 to 0; *P* = .043). However, this inverse association was attenuated after controlling for body mass index (β = –0.05; 95% CI, –0.13 to 0.02; *P* = .174). The mean follow-up period for cardiovascular disease events was 13.3 +/− 2.8 years. Additionally, exploratory analysis demonstrated that CAC density was independently and inversely associated with cardiovascular disease events only in the non-OSA subgroup (apnea-hypopnea index ≤ 15 events/h) (hazard ratio, 0.509; 95% CI, 0.323–0.801); *P* = .0035).

Conclusions: OSA was associated with lower CAC density, but this association was attenuated by body mass index. Further, increased CAC density was associated with a reduced risk of cardiovascular disease events only in individuals within the non-OSA group in exploratory analysis.

Keywords: coronary artery calcium, sleep apnea, atherosclerosis

Citation: Newman SB, Kundel V, Matsuzaki M, et al. Sleep apnea, coronary artery calcium density, and cardiovascular events: results from the Multi-Ethnic Study of Atherosclerosis. *J Clin Sleep Med*. 2021;17(10):2075–2083.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea (OSA) is associated with cardiovascular events, but there is limited knowledge regarding the mechanism by which OSA contributes to coronary atherosclerosis. OSA has been found to be associated with coronary artery calcium (CAC) score; however, the relationship between OSA and the individual components of the CAC score has not been described.

Study Impact: This study shows that in the relationship between OSA and CAC density, body mass index is an important confounder. Additionally, more studies are needed in order to better understand the relationship between CAC density and cardiovascular events.

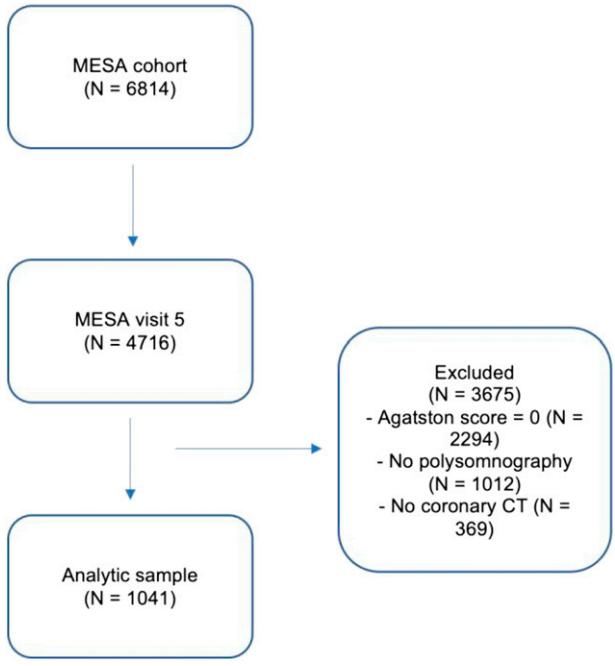
INTRODUCTION

Obstructive sleep apnea (OSA) is a common condition affecting 34% of men and 17% of women aged 30–70 years in the United States. Additionally, it also affects younger individuals with a prevalence of 3% among 30- to 39-year-old women and 10% among 30- to 39-year-old men.[1] Its effects include intermittent hypoxemia and sleep fragmentation, which are associated with increased sympathetic output resulting in hypertension,[2] increased inflammatory mediators,[3] endothelial dysfunction,[4] and insulin resistance.[5] These mechanisms, among others, are the basis by which OSA may lead to the acceleration of atherosclerosis and coronary artery disease. However, there have been mixed results in terms of treatment of OSA and reduction in cardiovascular events. Findings from numerous recent clinical trials have failed to demonstrate that treatment of OSA reduces the risk of cardiovascular (CV) events.[6,7] However, in the SAVE trial, when continuous positive airway pressure (CPAP) was used for 4 or more hours per night, there was a significant improvement in the risk of a cerebrovascular event.[8] As such, there is a need for mechanistic studies to aid our understanding of the differential effects of OSA on distinct vascular territories, specifically coronary atherosclerosis.

Coronary artery calcium (CAC) is a reliable measure of coronary atherosclerosis.[9] The Agatston (CAC) score is a composite of CAC area and density and is computed as the area of intravascular coronary calcium on computed tomography (CT) multiplied by the maximum density of the plaque calcification. A recent study by Criqui et al[10] within the Multi-Ethnic Study of Atherosclerosis (MESA) found that the CAC area and density were independently correlated with incident CV events; however, CAC density was *inversely* associated with CV events. In other words, the higher the CAC density, the lower the risk for CV events, and this held true for CAC density at any level of CAC area/volume.[11] This is because plaques that are larger and less dense are more prone to rupture; however, plaques that have stabilized over time are more densely calcified.

Prior studies evaluating the association between OSA and the Agatston score, including an earlier analysis of the MESA cohort,[12] have demonstrated that OSA is associated with higher CAC prevalence and Agatston score.[13,14] However, no published studies to our knowledge have assessed the association between OSA and CAC density, and how OSA influences the relationship between CAC density and incident CV events. We therefore conducted analyses in the MESA cohort to evaluate the independent association between OSA, CAC density, and cardiovascular events.

Figure 1—Flowchart of study participant inclusion and exclusion.



MESA = Multi-Ethnic Study of Atherosclerosis.

METHODS

Design

The Multi-Ethnic Study of Atherosclerosis is a cohort study comprising 6,814 men and women, ages 45–84 years at baseline in 2000–2002. Each participant was free of clinical cardiovascular disease (CVD) at the time of enrollment.[15] This is because one of the main objectives of the MESA cohort was to evaluate progression of subclinical atherosclerosis and CVD over time in asymptomatic individuals. Individuals with prior CVD may have residual culprit coronary atherosclerosis lesions that serve as a major confounder in evaluating the progression of subclinical CVD. The participants were recruited from 6 regions across the United States: Baltimore, Maryland; Chicago, Illinois; Los Angeles, California; New York, New York; St. Paul, Minnesota; and Winston-Salem, North Carolina. A total of 6 MESA visits have been completed to date with the fifth MESA occurring between April 2010 and January 2012.

A total of 4,716 participants took part in MESA visit 5, representing 78% of the total living MESA participants. Of this group, 2,500 individuals without clinical CVD (eg, myocardial infarction, angina, stroke, heart failure) underwent noncontrast coronary CT. Furthermore, 2,261 individuals not using CPAP or oral/dental appliances (for the treatment of OSA) or oxygen participated in the MESA Sleep ancillary study, which consisted of in-home polysomnography, actigraphy (up to 7 days), and a detailed sleep questionnaire. Our analytic sample included 1,041 individuals who completed a coronary CT and had a nonzero Agatston score, while also having a polysomnography measurement that allowed for calculation of the apnea-hypopnea index (AHI)[12] (**Figure 1**).

The institutional review board from each participating institution approved the MESA protocol, and all participants provided written informed consent. A detailed methodology of the MESA protocol has been described previously.[15]

Sleep measurement

In-home polysomnography was conducted using the Compumedics Somte System (Compumedics Ltd., Abbotsford, Victoria, Australia) and has been shown to be sufficient in comparison to in-laboratory polysomnography.[16] MESA utilized the standard protocol for an unattended full polysomnogram, which has been described previously.[16] During polysomnography, electroencephalography (central, occipital, and frontal), bilateral electrooculograms, chin electromyography, and thoracic and abdominal respiratory inductance plethysmography were utilized. Airflow was measured using a nasal-oral thermocouple and pressure-recording nasal cannula. In addition to these modalities, the MESA Sleep study recorded electrocardiograph, leg movements via piezoelectric sensors, and pulse oximetry. These recordings were sent to a centralized sleep center at Brigham and Women's Hospital and were scored by trained professionals. These technicians, who were centrally trained and blinded to the clinical data, scored the sleep studies with excellent inter- and intrascorer reliability ($r = .95–.99$).

OSA, defined as AHI ≥ 15 events/h, was calculated by adding all apneas to all hypopneas. Apneas were defined as a 90% reduction in the thermocouple signal lasting for 10 seconds or longer and were further distinguished as central or obstructive based on respiratory effort detected using inductance plethysmography.

Hypopneas were defined as a 30% or more reduction in amplitude of nasal pressure flow signal for 10 seconds or longer in association with at least a 4% desaturation. Both apnea and hypopnea episodes were divided by the total sleep duration. Arousals were defined as waking within 10 seconds from an apneic/hypopneic event as defined by the American Academy of Sleep Medicine (AASM).[17] Sleep stages were defined during each 30-second epoch by AASM criteria.[18] Other measures of sleep-disordered breathing collected were: average oxygen saturation, minimum oxygen saturation, percent time with < 90% saturation, percent time with apnea/hypopnea, percent time in slow-wave (N3) sleep, percent time in rapid eye movement sleep, sleep duration, and arousal index in rapid eye movement and non-rapid eye movement sleep.

CAC measurement

Electron-beam CT was used in 3 locations (Chicago, Los Angeles, and New York), and multidetector CT was used at the other 3 locations (Baltimore, St. Paul, and Winston-Salem). Electron-beam CT slices were 3.0-mm thick, and multidetector CT slices were 2.5-mm thick. All CT scans were cardiac-gated, phantom-adjusted, and read centrally by 2 trained analysts. CAC measurements were obtained by the standardized MESA protocol as described previously[19] and utilized the Agatston method.[20] More specifically, a CAC lesion was defined as an intracoronary plaque of at least 4 contiguous pixels (area > 1 mm^2) with a minimum Hounsfield unit attenuation > 130 HU. The total number of lesions within a plaque were then summed to obtain the plaque area. The area was then multiplied by a density weighting factor defined as the maximum HU attenuation within an individual plaque (1–4: 1 = 130–199, 2 = 200–299, 3 = 300–399, 4 = 400 or greater). The sum of the plaque areas, upweighted for the maximum density within each plaque, represented the Agatston score. The CAC volume was calculated by multiplying the sum of the plaque areas by the CT slice thickness. The CAC density was then calculated by dividing the Agatston score by the total area score.[11]

CVD events

CVD events were defined as myocardial infarction, resuscitated cardiac arrest, coronary heart disease death, transient ischemic attack, stroke, or stroke death. The follow-up period for CVD events began at the time of the baseline examination and continued until the first CVD event, death, loss to follow-up, or calendar year 2015. Details on the MESA study's follow-up methods and event adjudication are available on the MESA website at https://www.mesa-nhlbi.org.

Other variables

The detailed questionnaires and clinic examination methods for the MESA exams have been described previously.[12] Briefly, sex (male or female), age (as continuous variable), cigarette smoking (current, former < 1 year since cessation, former ≥ 1 year since cessation, never), use of cholesterol-lowering medication (yes/no), use of antihypertensive medication (yes/no), alcohol (yes/no), and race (categorized into non-Hispanic White, Black, Hispanic, and Chinese American) were self-reported.

Anthropometric measurements were obtained in the clinic and used to calculate body mass index (BMI), defined as weight (kg) over height (m) squared (kg/m^2). Resting blood pressure was measured 3 times using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida), and the average of the last 2 measurements was used for blood pressure calculation. The presence of hypertension was defined as a dichotomous yes/no variable based on the sixth report of the Joint National Committee guidelines (systolic blood pressure > 140 or diastolic blood pressure > 90 mm Hg),[21] or by use of antihypertensive medications. The presence of chronic kidney disease (CKD) was defined as a dichotomous yes/no variable using the *CKD-EPI* eGFR equation with a cutoff value of < 60 mL/min/1.73 m^2.[22]

Participants were required to fast for 8 hours prior to their visit. High-density lipoprotein (mg/dL) was assessed in ethylenediamine tetraacetic acid (EDTA) plasma using the cholesterol oxidase method (Roche Diagnostics, Basel, Switzerland). Next, precipitated non–high-density lipoprotein was assessed with magnesium/dextran. Low-density lipoprotein cholesterol (mg/dL) was calculated among those having triglycerides < 400 mg/dL using the Friedewald formula. We defined dyslipidemia as a dichotomous yes/no variable based on a low-density lipoprotein level ≥ 160 mg/dL, high-density lipoprotein level < 40 mg/dL in men and < 50 mg/dL in women, triglycerides ≥ 150 mg/dL, or use of statins. We defined glucose dysregulation according to the 2003 American Diabetes Association fasting criteria, which contains 4 categories: normal (fasting plasma glucose [FPG] < 100 mg/dL), impaired FPG levels (100 mg/dL to 125 mg/dL), treated DM (FPG < 100 mg/dL with prior diagnosis of DM), and untreated DM (FPG ≥ 126 mg/dL) as measured by reflectance spectrophotometry using thin film adaptation of the glucose oxidase method on the VITROS analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY).[23]

Statistical analysis

Based on a clinically relevant cutoff for OSA that has been previously linked to CVD risk,[24] the study population consisted of individuals with nonzero Agatston scores and was stratified by none-to-mild OSA (AHI < 15 events/h) or OSA (AHI ≥ 15 events/h). Individuals with Agatston scores of zero were excluded because CAC density can only be derived from nonzero CAC values. We present descriptive characteristics using means and standard deviations for continuous variables and percentages for categorical variables. The 2 AHI groups were compared using *t* tests (continuous variables) or χ^2 tests (categorical variables). We then utilized analysis of covariance–adjusted means and Tukey's posthoc test for adjusted means.

We developed 3 multivariable linear regression models. These were used to compare OSA (dichotomous) or AHI (continuous) to CAC density. Defining OSA as a dichotomous variable (AHI < 15 or ≥ 15 events/h) allows for differentiation between mild OSA and moderate-to-severe OSA, whereas AHI as a continuous variable allows for more finely assessing a dose-response relationship. Model 1 was adjusted for age, sex, and race/ethnicity; model 2, adjusted for model 1 plus hypertension, dyslipidemia, glucose dysregulation/diabetes, and smoking status; model 3 controlled

for model 2 plus BMI. Formal testing for multiplicative interaction in separate models (interaction between OSA and sex (SA*sex), obesity, and statin use) was conducted to evaluate whether the independent association between OSA/AHI and CAC density varied by sex, obesity, or statin use with a predefined *P* value of < .1.

Cox proportional hazard regression models were used to estimate hazard ratios for time to CVD events for Agatston CAC score, density score, and volume score, adjusting for atherosclerotic cardiovascular disease risk score in individuals who had polysomnography.[25] The Agatston and volume scores were log-transformed since previous MESA analyses have demonstrated log linear relationships between CAC and CVD risk.[26] Since CAC volume and density are strongly positively correlated, we mutually adjusted for these variables in our statistical models. Results were stratified by none-to-mild OSA (AHI < 15 events/h) or moderate-to-severe OSA (AHI ≥ 15 events/h). Additionally, we also tested for multiplicative interaction for OSA*CAC density, Agatston score, and volume to evaluate whether CVD events varied by OSA status. Analyses for regression models were conducted at the .05 2-sided significance level. Statistical significance for multiplicative interaction was predefined at a *P* value < .1. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics

Baseline characteristics are shown in **Table 1**. The overall prevalence of moderate-to-severe OSA (AHI ≥ 15 events/h) in our sample was 36.7% (n = 383). The mean age was 70.7 ± 9.1 years in none-to-mild OSA and 70.4 ± 9.0 years in moderate-severe OSA individuals. As expected, male sex, higher BMI, higher diastolic blood pressure, impaired FPG, lower high-density lipoprotein, and higher triglycerides (*P* < .01) were more common in individuals with OSA. The average Agatston score (*P* = .92), CAC density (*P* = .14), and CAC volume (*P* = .87) were not statistically different between the OSA severity groups. When adjusting these means for age, sex, and race using analysis of covariance, and performing a comparison utilizing Tukey's post-hoc test, we did not find significant differences in any of the CAC measures by OSA status.

The associations between OSA/AHI and Agatston score after multivariable regression analysis can be found in **Table 2**. There were no statistically significant associations between OSA (dichotomous) and AHI (continuous) and Agatston score in any of the models. These associations did not vary significantly by sex, obesity, or statin use.

OSA and CAC density

Multivariable regression models for the association between OSA and CAC density are shown in **Table 3**. Measured as a continuous variable, AHI was modestly inversely associated with CAC density in model 1 (β = –0.04; 95% CI, –0.08 to –0.01; *P* = .02). This association became nonsignificant in model 2 (β = –0.04; 95% CI, –0.08 to 0; *P* = .07) and further attenuated in model 3 (β = –0.02; 95% CI, –0.06 to 0.02; *P* = .34). Similarly, OSA measured as a dichotomous variable (AHI < 15 or ≥ 15 events/h) was inversely associated with CAC density in models 1 (β = –0.09; 95% CI, –0.17 to –0.02; *P* = .01), and 2 (β = –0.08; 95% CI, –0.16 to 0.00; *P* = .04). However, this association was attenuated in model 3 after adjusting for BMI (β = –0.05; 95% CI, –0.13 to 0.02; *P* = .17). Therefore, compared to those with none-to-mild OSA (AHI < 15 events/h), individuals with OSA (AHI ≥ 15 events/h) would on average have an 8% lower CAC density when controlling for cardiovascular risk factors, excluding BMI.

The associations between OSA and CAC density did not vary by sex (OSA continuous [*P* = .22], OSA dichotomous [*P* = .79]), or obesity/BMI level (OSA continuous [*P* = .36], OSA dichotomous [*P* = .41]). However, there was an interaction between OSA and statin use (OSA continuous [*P* = .09], OSA dichotomous [*P* = .09]). When stratified by statin use, OSA (dichotomous, AHI ≥ 15 events/h) was inversely associated with CAC density in individuals *not* on statins even after adjusting for confounders (β = –0.14; 95% CI, –0.26 to –0.03; *P* = .013), although further adjustment for BMI resulted in attenuation of this signal (β = –0.11; 95% CI, –0.22 to 0.01; *P* = .07) (**Table 4**). In comparison, there was no evidence of an association among those taking statin medications (β = 0.01; 95% CI, –0.09 to 0.12; *P* = .78). Therefore, compared to individuals with OSA *on* statins, individuals with OSA *not* on statins had a CAC density that was 0.11 lower on average, even after controlling for cardiovascular risk factors.

CAC density and CVD events

Among those who had polysomnography data, there was a total of 160 CVD events. The mean follow-up period for CVD events was 13.3 +/− 2.8 years. *P* interaction values for OSA with CAC density, Agatston score, and volume to evaluate whether CVD events varied by OSA status were not significant (*P* > .10). However, we conducted an exploratory analysis to further stratify CVD events by OSA severity. Adjusted hazard ratios for CAC density, Agatston score, CAC volume, and CVD events are shown in **Table 5**. In patients with none-to-mild OSA, increasing CAC density conferred almost a 50% reduced risk of CVD events (hazard ratio, 0.509; 95% CI, 0.323–0.801; *P* = .0035) after adjusting for atherosclerotic cardiovascular disease score. While this relationship held true in participants with moderate-to-severe OSA, it was attenuated and did not reach statistical significance for CVD events (hazard ratio, 0.783; 95% CI, 0.434–1.410; *P* = .4146). On the other hand, both increasing Agatston score and CAC volume were associated with an increased risk of CVD events regardless of OSA severity.

DISCUSSION

In this large, racially diverse community-based sample, we found an inverse association between OSA and CAC density, which was partially attenuated after adjusting for cardiovascular risk factors, especially BMI. When stratified by statin use, there was an apparent influence of statins on the association between OSA and CAC density such that OSA appeared to be associated with lower CAC density only in statin nonusers. These results indicate that obesity

Table 1—Characteristics of the study participants with or without sleep apnea (apnea-hypopnea index < 15 or ≥ 15 events/h).

	AHI < 15 events/h (n = 658)	AHI ≥ 15 events/h (n = 383)	Comparison Tests
Age (y)	70.7 (9.1)	70.4 (9)	0.58
Sex, n (%)			< 0.01
Female	347 (52.7)	125 (32.6)	
Male	311 (47.3)	258 (67.4)	
Race/ethnicity, n (%)			< 0.01
White/Caucasian	265 (40.3)	138 (36)	
Chinese American	64 (9.7)	50 (13.1)	
Black/African American	183 (27.8)	81 (21.1)	
Hispanic	146 (22.2)	114 (29.8)	
Education, n (%)			0.34
Less than high school	91 (13.9)	59 (15.4)	
High school	316 (48.1)	194 (50.7)	
College	108 (16.4)	65 (17)	
Graduate school	142 (21.6)	65 (17)	
Body mass index (kg/m^2)	27.9 (4.8)	30.4 (5.5)	< 0.01
Systolic blood pressure (mm Hg)	124.2 (20.7)	125.3 (19.7)	0.38
Diastolic blood pressure (mm Hg)	67.8 (10.1)	69.4 (9.6)	< 0.01
Hypertension (yes), n (%)*	413 (62.7)	252 (65.8)	0.36
eGFR < 60 (yes), n (%)	99 (15.1)	49 (12.9)	0.33
Dyslipidemia (yes), n (%)†	406 (61.7)	259 (67.2)	0.06
LDL (mg/dL)	104 (31.5)	102.2 (31.8)	0.36
HDL (mg/dL)	56.6 (16.8)	50.7 (13.2)	< 0.01
Triglycerides (mg/dL)	107.1 (64.2)	120.1 (64.8)	< 0.01
Statin use (yes), n (%)	275 (41.8)	176 (46.0)	0.21
Diabetes, n (%)			< 0.01
Normal	386 (58.8)	175 (46.1)	
Impaired fasting glucose	139 (21.2	99 (26.1)	
Treated diabetes	118 (18)	101 (26.6)	
Untreated diabetes	13 (2)	5 (1.3)	
CAC Agatston score‡	410.5 (737.3)	457.9 (766.4)	0.92
CAC density§	3.13 (0.73)	3.06 (0.75)	0.14
CAC volume (mm^3)	313.6 (522.9)	357.8 (561.7)	0.87
Smoking status, n (%)‖			0.11
Current smoker	51 (7.8)	17 (4.5)	
Former	260 (40)	156 (41.3)	
Never smoked	339 (52.2)	205 (54.2)	
Smoking pack y	12.1 (22)	10.5 (19.1)	0.24
Alcohol consumption (yes), n (%)	288 (44)	178 (46.7)	0.43

All values are mean (standard deviation) or counts (percentage). The 2 AHI groups were compared using *t* tests (continuous variables) or χ^2 tests (categorical variables). The comparisons for CAC variables were adjusted for age, sex, and race. The numbers were updated on October 27, 2017 as we only wanted to include participants who had AHI and valid CAC density scores. *Hypertension was defined as a dichotomous yes/no variable based on the sixth report of the Joint National Committee guidelines (systolic blood pressure > 140 or diastolic blood pressure > 90 mm Hg).[21] †Dyslipidemia was defined as a dichotomous yes/no variable based on a low-density lipoprotein level ≥ 160 mg/dL, high-density lipoprotein level < 40 mg/dL in men and < 50 mg/dL in women, triglycerides ≥ 150 mg/dL, or use of statins. ‡The score was adjusted for the participants whose CAC measurement was done on machines with a slice thickness of 2.5 mm. §CAC density was calculated by dividing Agatston score by CAC area; for a slice thickness of 2.5 mm, CAC area = CAC volume/2.5; for 3 mm, CAC area = CAC volume/3. ‖Includes 2 former categories (< and ≥ 1 year since cessation). AHI = apnea-hypopnea index, CAC = coronary artery calcium, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 2—Multivariable association between Agatston score and AHI (continuous) or sleep apnea (binary; AHI < 15 or ≥ 15 events/h).

	Predictor	Model 1		Model 2		Model 3	
		β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Agatston score	Continuous AHI	0.02 (–0.02 to 0.06)	.268	0.01 (–0.03 to 0.05)	.754	0.00 (–0.05 to 0.04)	.821
	OSA (yes vs no)	0.02 (–0.06 to 0.1)	.663	0.00 (–0.08 to 0.08)	.97	–0.02 (–0.1 to 0.07)	.71

The following variables were standardized: AHI (log-transformed first), CAC volume (log-transformed first), age, HDL, NREM sleep arousal index. Model 1 = Agatston score (and density) ~ AHI (or OSA) (+ CAC volume if outcome = density) + age + sex + race/ethnicity. Model 2 = Agatston score (and density) ~ model 1 + HTN + dyslipidemia + diabetes + smoking status. Model 3 = Agatston score (and density) ~ model 2 + body mass index. AHI = apnea-hypopnea index, CAC = coronary artery calcium, CI = confidence interval, HDL = high-density lipoprotein, HTN = hypertension, NREM = nonrapid eye movement, OSA = obstructive sleep apnea.

Table 3—Multivariable association between CAC density and AHI (continuous) or sleep apnea (binary; AHI < 15 or ≥ 15 events/h).

Predictor	Model 1		Model 2		Model 3	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Continuous AHI	–0.04 (–0.08 to –0.01)	.023	–0.04 (–0.08 to 0.00)	.068	–0.02 (–0.06 to 0.02)	.348
OSA (yes vs no)	–0.09 (–0.17 to –0.02)	.014	–0.08 (–0.16 to 0.00)	.043	–0.05 (–0.13 to 0.02)	.174

The following variables were standardized: AHI (log-transformed first), CAC volume (log-transformed first), age, HDL, NREM sleep arousal index. Model 1 = Agatston score (and density) ~ AHI (or OSA) (+ CAC volume if outcome = density) + age + sex + race/ethnicity. Model 2 = Agatston score (and density) ~ model 1 + HTN + dyslipidemia + diabetes + smoking status. Model 3 = Agatston score (and density) ~ model 2 + body mass index. AHI = apnea-hypopnea index, CAC = coronary artery calcium, CI = confidence interval, HDL = high-density lipoprotein, HTN = hypertension, NREM = nonrapid eye movement, OSA = obstructive sleep apnea.

Table 4—Multivariable association between CAC density and AHI (continuous) or sleep apnea (binary; AHI ≥ or < 15 events/h), stratified by statin use.

Statin Use	Predictor	Model 1		Model 2		Model 3	
		β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Yes	AHI	–0.01 (–0.07 to 0.05)	.739	0.01 (–0.05 to 0.06)	.743	0.02 (–0.04 to 0.08)	.598
	OSA (yes)	–0.04 (–0.14 to 0.07)	.488	0.01 (–0.1 to 0.11)	.894	0.01 (–0.09 to 0.12)	.782
No	AHI	–0.07 (–0.12 to –0.02)	.01	–0.07 (–0.12 to –0.01)	.02	–0.04 (–0.1 to 0.02)	.157
	OSA (yes)	–0.13 (–0.24 to –0.03)	.016	–0.14 (–0.26 to –0.03)	.013	–0.11 (–0.22 to 0.01)	.069

The following variables were standardized: AHI (log-transformed first), CAC volume (log-transformed first), age, HDL, NREM sleep arousal index. Model 1 = Agatston score (and density) ~ AHI (or OSA) (+ CAC volume if outcome = density) + age + sex + race/ethnicity. Model 2 = Agatston score (and density) ~ model 1 + HTN + dyslipidemia + diabetes + smoking status. Model 3 = Agatston score (and density) ~ model 2 + body mass index. AHI = apnea-hypopnea index, CAC = coronary artery calcium, CI = confidence interval, HDL = high-density lipoprotein, HTN = hypertension, NREM = nonrapid eye movement, OSA = obstructive sleep apnea.

Table 5—Adjusted hazard ratios for CAC scores and cardiovascular disease events stratified by sleep apnea severity (binary; AHI ≥ or < 15 events/h).

	CVD			
	AHI < 15 events/h (n = 92)		AHI ≥ 15 events/h (n = 68)	
	HR* (95% CI)	P	HR* (95% CI)	P
CAC density	0.509 (0.323–0.801)	.0035	0.783 (0.434–1.410)	.4146
Agatston score	1.427 (1.238–1.644)	< .01	1.447 (1.221–1.715)	< .01
CAC volume	1.786 (1.478–2.158)	< .01	1.617 (1.270–2.058)	< .01

Adjusted for atherosclerotic cardiovascular disease (ASCVD) risk score. *Agatston and volume scores were log-transformed. AHI = apnea-hypopnea index, CAC = coronary artery calcium, CI = confidence interval, CVD = cardiovascular disease, HR = hazard ratio, OSA = obstructive sleep apnea.

is an important and key confounder in the relationship between OSA and CAC density, and that statins may serve as effect modifiers in the relationship between OSA and CAC density. Additionally, in an exploratory analysis we found that increasing CAC density showed an inverse association with CVD events—but only in those with no or mild OSA. This is hypothesis-generating and potentially suggests that CAC density may be less protective for CVD events in those with moderate-to-severe OSA.

Prior studies have demonstrated that OSA is associated with subclinical atherosclerosis.[27] However, its association with coronary artery disease is equivocal, with data from the largest trial revealing higher coronary revascularization rates among those randomized to OSA treatment with continuous positive airway pressure.[8] As such, there is a need for mechanistic studies to aid our understanding of the effect of OSA on coronary atherosclerosis. To address this gap in knowledge, several studies have examined the effect of OSA on Agatston score. One study by Weinreich et al[14] found that OSA was associated with a higher Agatston score, but this was only significant in women, as well as men age < 65. More recently, another publication also utilizing the MESA cohort found that severe OSA (AHI ≥ 30 events/h) was associated with a higher prevalence of CAC (CAC > 0).[12] However, the association between OSA and CAC *density* was not analyzed.

Ours is the first study to analyze the association between OSA and the *individual* components of the Agatston score. While the Agatston score is widely used as a reliable predictor for future CV risk, this score assumes that both CAC density and CAC area/volume are positively correlated with future CVD risk. This seemingly contradicts the pathophysiology of coronary atheroma progression. That is, as atheromas stabilize, histological evidence has shown a greater deposition of dense sheets of calcification,[28] which may increase plaque density and stability. In this regard, and as demonstrated by Criqui et al,[10] greater CAC density was associated with a *lower* CVD risk, implying plaque stabilization. They also found that utilizing CAC density significantly increased the accuracy of CVD risk prediction,[11] suggesting that measuring CAC density separately when studying subclinical coronary artery disease may provide a more accurate CV risk profile in patients with OSA.

Our results demonstrated an inverse relationship between OSA and CAC density that was attenuated after adjusting for traditional cardiovascular risk factors, including BMI. Similar to our results, prior studies examining the association between OSA and Agatston score have also identified BMI as an important confounder.[12] For instance, Kim et al[29] found that AHI was positively correlated with Agatston score (odds ratio, 2.2; 95% CI, 1.01–4.86), but this association was no longer significant when controlling for BMI (odds ratio, 1.16; 95% CI, 0.49–2.74). The relationship between OSA and BMI is indeed complex. This is because obesity is a well-established risk factor for many of the cardiovascular outcomes of interest, including intermediate outcomes such as CAC density. Therefore, BMI has typically been regarded as a potential confounder in the relationship between OSA and CVD.

Statins, once thought to promote plaque retrogression, may in fact stabilize coronary plaques by increasing coronary plaque density.[30] This concept is further supported by histopathological studies of coronary atheromas, in which plaques with diffuse sheets of dense calcium deposits are stable and more likely to be seen in healing coronary plaques.[28] Budoff et al[31] demonstrated that statin use was unexpectedly associated with a higher Agatston score. The authors speculated that use of statins leads to reduced lipid content in plaques, resulting in a higher CAC density and Agatston score. Therefore, our results may suggest that the adverse effects of OSA on CAC density may be attenuated by statin use, though further investigations are warranted to confirm these findings.

Last, we replicated the findings from Criqui et al[11] in our exploratory analyses, which show that increased CAC density is protective against CVD events in individuals with none-to-mild OSA, although the hazard ratio is attenuated and not statistically significant in individuals with moderate-to-severe OSA. These results are hypothesis-generating, and potentially suggest that moderate-to-severe OSA may confer an alternate effect on the coronary atherosclerotic cascade, resulting in lower CAC density in those with OSA. Alternatively, the lack of statistical significance in the OSA subgroup may be secondary to limited sample size. In contrast to CAC density, increased Agatston score and CAC volume conferred an increased risk of CVD events regardless of OSA severity,[11] in the same sample size. Therefore, it is possible that OSA may have modulating effects on the prognostic implications of CAC density.

Our study has several limitations. First, the OSA and CAC measurement components of our study provided a cross-sectional analysis, and therefore causal inference cannot be made. Second, as with any cross-sectional studies, our analysis may have been subject to temporal and survival bias. Third, we excluded individuals without CAC (CAC = 0); therefore, the associations of OSA with noncalcified plaques (early calcification) were not assessed in this study. Fourth, our study excluded individuals with prior CVD by default, as the MESA cohort only recruited those individuals free of clinical CVD at baseline. This may potentially limit the generalizability of our results to individuals with prior CV events. Moreover, the mean age of the sample was significantly higher than prior studies, rendering our results less generalizable to middle-aged individuals. Given that the association between OSA and CAC density and/or CVD events may be altered as other comorbidities become more prevalent in older populations, we adjusted for age in all of our analyses to account for potential confounding. Further, survivorship bias may have affected our study as our cross-sectional analysis inherently applies only to survivors. We also did not account for CPAP use during the CVD event follow-up period. This is because the MESA cohort database does not include prospective CPAP adherence data. This may influence the rate of CVD events, and future studies should assess the association between CAC density and CVD events in OSA stratified by CPAP use. Last, multiplicative interactions with OSA and CVD events were not significant, therefore the results of our exploratory analysis investigating the association between CVD events stratified by OSA severity are hypothesis-generating and require further investigation in future studies.

In conclusion, we found that there is an inverse association between OSA and CAC density that is attenuated by BMI. This highlights that BMI—a prognostic indicator of CV health—is an important confounder in studies examining the link between OSA and CAC. Moreover, there is possible effect modification by statins. Further, we demonstrate in an exploratory analysis that while CAC density independently confers protection against CVD events in the none-to-mild OSA subgroup, it may not offer the same protection in individuals with more severe OSA. Further investigation in larger samples is necessary to determine the independent influence of mild, moderate, and severe OSA on coronary plaque calcification and density, the role of statin therapy as an effect modifier, and their implications for cardiovascular outcomes.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CAC, coronary artery calcium
CPAP, continuous positive airway pressure
CT, computed tomography
CV, cardiovascular
CVD, cardiovascular disease
FPG, fasting plasma glucose
MESA, Multi-Ethnic Study of Atherosclerosis
OSA, obstructive sleep apnea

REFERENCES

1. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* 2013;177(9):1006–1014.
2. Pedrosa RP, Drager LF, de Paula LKG, Amaro ACS, Bortolotto LA, Lorenzi-Filho G. Effects of OSA treatment on BP in patients with resistant hypertension: a randomized trial. *Chest.* 2013;144(5):1487–1494.
3. Minoguchi K, Yokoe T, Tanaka A, et al. Association between lipid peroxidation and inflammation in obstructive sleep apnoea. *Eur Respir J.* 2006;28(2):378–385.
4. Khayat RN, Varadharaj S, Porter K, et al. Angiotensin receptor expression and vascular endothelial dysfunction in obstructive sleep apnea. *Am J Hypertens.* 2018; 31(3):355–361.
5. Martínez-Cerón E, Barquiel B, Bezos AM, et al. Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes. A randomized clinical trial. *Am J Respir Crit Care Med.* 2016;194(4):476–485.
6. Barbé F, Durán-Cantolla J, Capote F, et al; Spanish Sleep and Breathing Group. Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med.* 2010;181(7):718–726.
7. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med.* 2016;194(5):613–620.
8. McEvoy RD, Antic NA, Heeley E, et al; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med.* 2016;375(10):919–931.
9. Budoff MJ, Georgiou D, Brody A, et al. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study. *Circulation.* 1996;93(5):898–904.
10. Criqui MH, Denenberg JO, Ix JH, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. *JAMA.* 2014;311(3):271–278.
11. Criqui MH, Knox JB, Denenberg JO, et al. Coronary artery calcium volume and density: potential interactions and overall predictive value: the Multi-Ethnic Study of Atherosclerosis. *JACC Cardiovasc Imaging.* 2017;10(8):845–854.
12. Lutsey PL, McClelland RL, Duprez D, et al. Objectively measured sleep characteristics and prevalence of coronary artery calcification: the Multi-Ethnic Study of Atherosclerosis Sleep study. *Thorax.* 2015;70(9):880–887.
13. Luyster FS, Kip KE, Aiyer AN, Reis SE, Strollo PJ Jr. Relation of obstructive sleep apnea to coronary artery calcium in non-obese versus obese men and women aged 45-75 years. *Am J Cardiol.* 2014;114(11):1690–1694.
14. Weinreich G, Wessendorf TE, Erdmann T, et al; Heinz Nixdorf Recall (HNR) study group. Association of obstructive sleep apnoea with subclinical coronary atherosclerosis. *Atherosclerosis.* 2013;231(2):191–197.
15. Bild DE, Bluemke DA, Burke GL, et al; Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol.* 2002;156(9):871–881.
16. Redline S, Sanders MH, Lind BK, et al; Sleep Heart Health Research Group. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. *Sleep.* 1998;21(7):759–767.
17. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep.* 1992;15(2):173–184.
18. Silber MH, Ancoli-Israel S, Bonnet MH, et al. The visual scoring of sleep in adults. *J Clin Sleep Med.* 2007;3(2):121–131.
19. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. *Radiology.* 2005;234(1):35–43.
20. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990;15(4):827–832.
21. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med.* 1997;157(21):2413–2446.
22. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604–612.
23. Genuth S, Alberti KG, Bennett P, et al; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care.* 2003;26(11):3160–3167.
24. Jones A, Vennelle M, Connell M, et al. The effect of continuous positive airway pressure therapy on arterial stiffness and endothelial function in obstructive sleep apnea: a randomized controlled trial in patients without cardiovascular disease. *Sleep Med.* 2013;14(12):1260–1265.
25. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(25 suppl 2):S49–S73.
26. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med.* 2008;358(13):1336–1345.
27. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2005;172(5):613–618.
28. Lutter C, Joner M. Pathologic correlates in stable coronary plaques. Traditional and novel insights from pathology. *Contin Cardiol Educ.* 2016;2(2):56–65.
30. Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol.* 2015;65(13):1273–1282.
31. Budoff MJ, Young R, Lopez VA, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol.* 2013;61(12):1231–1239.

ACKNOWLEDGMENTS

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at https://www.mesa-nhlbi.org.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December 15, 2020
Submitted in final revised form April 15, 2021
Accepted for publication April 15, 2021
Address correspondence to: Neomi A. Shah, MD, MPH, MS, Icahn School of Medicine at Mount Sinai, Division of Pulmonary, Critical Care and Sleep, One Gustave L. Levy Place, Box 1232, New York, NY 10029; Tel: (212) 241-6286; Fax: (212) 876-5519; Email: Neomi.shah@mssm.edu

DISCLOSURE STATEMENT

All authors have seen and approved the current version of the manuscript. Work was performed at the Icahn School of Medicine at Mount Sinai, New York, NY. This research was supported by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR–000040, UL1-TR–001079, and UL1-TR–001420 from the National Center for Advancing Translational Sciences (NCATS). This publication was developed under the Science to Achieve Results (STAR) research assistance agreements, No. RD831697 (MESA Air) and RD-83830001 (MESA Air Next Stage), awarded by the US Environmental Protection Agency. It has not been formally reviewed by the EPA. The views expressed in this document are solely those of the authors and the EPA does not endorse any products or commercial services mentioned in this publication. S.B.N, V.K., M.M., M.R., J.R.K., R.C.K., Z.A.F., V.M., S.S., M.A., M.C., P.L.L., R.L.M., and N.A.S. report no conflicts of interest. S.R. reports receiving grants and consulting funds from Jazz Pharmaceuticals and consulting fees from Eisai Pharmaceuticals, unrelated to this project. J.R.K. reports stock ownership in Bristol Myers Squibb, Johnson & Johnson, Medtronic, Merck, and Pfizer.