SLEEP APNEA AND PROGRESSION OF CORONARY ARTERY CALCIUM:
THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

A Thesis
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Dedication

This thesis is dedicated to my dear wife Yeilim and lovely children, Jamie, Jason and Jane who all remind me of the purpose of this life

Abstract

Background: Obstructive sleep apnea (OSA) is a common condition believed to be linked to cardiovascular comorbidities. Its potential effect on progression of subclinical atherosclerosis is not well studied. We tested the hypothesis that OSA is associated with progression of coronary artery calcium (CAC) score. We also evaluated whether traditional cardiovascular risk factors mediated the association.

Methods: The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective epidemiologic cohort which has had a total of 5 clinic visits. Our primary analytic sample included 2,603 participants who at or near visit 2 (2002-2004) completed a sleep questionnaire and underwent coronary computerized tomography (CT), and underwent a repeat coronary CT approximately 8 years later (Visit 5: 2010-2011). Participants were categorized by their self-reported sleep breathing history: OSA: n= 102; Habitual snore: n = 666; Normal: n= 1835. mean age: 61.2).

Results: Absolute CAC scores varied at visit 2, with the highest CAC prevalence among those with OSA, and lower but similar CAC prevalences among those who were habitual snorers or normal. Over 8 years of follow-up, greater progression of CAC was observed among those with OSA vs. those classified as normal (mean increase of 227.7 vs.135.6 Agatston units). This difference persisted after adjustment for BMI but was not significant after adjustment for cardiovascular risk factors (138.2 vs. 185.9 Agatston units; p = 0.08). CAC progression among habitual snorers was similar to that observed in the normal group.

Conclusion: Self-reported sleep apnea was associated with CAC score progression after adjustment for demographics, behaviors and BMI. However, the association was not significant after accounting for cardiovascular risk factors which may mediate the association between OSA and CAC.

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Background

Obstructive sleep apnea (OSA) is a common condition, estimated to be prevalent in at least 3-7% of the adult population in developed countries.[1] Beyond poor quality of sleep and its directly related symptoms, an emerging body of evidence links OSA to a more adverse cardiovascular risk factor profile and increased risk of cardiovascular disease (CVD) events.[2,3] Individuals who snore are known to have a disproportionately higher prevalence of undiagnosed OSA than those who do not snore,[4] and snoring has also been associated with higher risk of CVD risk factors and events.[5-7]

In an effort to better understand the relation between OSA and CVD, examining the association between OSA and subclinical coronary atherosclerotic change may be valuable.[8] Coronary artery calcium (CAC) assessed by coronary computerized tomography (CT) is a well-established surrogate marker that has been shown to be predictive of future coronary events in numerous studies.[9,10]

Results have been inconsistent among the relatively few studies that have directly explored the association between OSA and CAC prevalence.[11-15] To date, no studies have assessed the longitudinal association of OSA with change in CAC. In this study, we tested a hypothesis that over 8 years of follow-up participants with OSA would have a more pronounced increase in CAC, relative to participants who do not snore in a racially/ethnically diverse population free of overt CVD. We anticipated that participants who self-reported snoring would have an intermediate increase in CAC. The cross-sectional association between self-reported OSA and CAC prevalence is also reported.

Methods

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of 6,814 community-dwelling men and women aged 45–84 years without evidence of cardiovascular disease at baseline (2000-2002). Participants were recruited from 6 U.S. communities (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles County, CA) and self-identified as White, Chinese, Black or Hispanic.[16] A total of 6,232 participants attended MESA Exam 2 (September 2002- February 2004), of whom 5,395 completed the sleep history questionnaire. Among those who completed the sleep questionnaire, 4,919 underwent coronary CT at exam 2, or had coronary CT at both exam 1 (June 2000-August 2002) and 3 (March 2004 – September 2005), thereby allowing us to derive interpolated exam 2 CAC. These participants made up our "parent cohort". We required that for the main analysis of CAC change, participants also attend MESA visit 5 coronary CT (April 2010- December 2011; attended by 55 % of the parent cohort). After excluding participants with a history of revascularization and one participant with apparent CAC measurement error, our final analytic sample included 2,603 participants ("final cohort"). The research protocols were approved by the Institutional Review Boards at each participating Institution and all participants gave written informed consent. Detailed descriptions of the study design and methods of MESA have been published previously.[16]

Sleep Breathing History

A self-administered sleep history questionnaire conducted at exam 2 included the following 3 key questions regarding sleep breathing history: a) (Physician diagnosed sleep apnea question); Have you ever been told by a doctor that you had sleep apnea? b) (Snoring question) Have you ever snored (now or at any time in the past)? ; c) (Snoring frequency question) How often do you snore now? Figure 1 illustrates construction of 3 sleep breathing group (OSA, Habitual snoring, Normal) based on the response to these questions. Since OSA (vs. central sleep apnea) is by far the most common form of sleep apnea in the absence of heart failure or stroke, we considered self-reported physician diagnosed sleep apnea to be OSA in this study. In addition, information on subjective perception of excessive daytime sleepiness was extracted from the question: How often do you feel excessively (overly) sleepy during the day? This information was used to test for potential effect modification. Participants who responded "never /rarely" (1 day/ month or less) or "sometimes" (2-4 days/month) were considered not to have excessive daytime sleepiness. Those who responded "often" (5-15 days/month) or "almost always" (16-30 days/ month) were considered to have excessive daytime sleepiness.

Coronary artery calcium

Details of the technique and methodology of the scans and approach to quantifying CAC have been previously published.[17]. Briefly, CAC imaging was conducted using either electron-beam (EBT; Imatron C-150; Imatron, San Francisco, California) or multidetector CT (MDCT; Lightspeed, General Electric Medical System, Waukesha, Wisconsin; or Volume Zoom, Siemens, Erlanger, Germany). CT images were acquired

by a certified technologist and read by a trained physician-reader at a centralized reading center (Los Angeles Biomedical Research Institute, Torrance, California). CAC scores were quantified by the Agatston method[18] from two consecutively obtained CT scans at each visit and average CAC scores were obtained. CAC scores were subsequently adjusted with a standard calcium phantom that was scanned along with the participant.[17] Excellent inter- and intra-observer agreement were found based on the kappa statistics (k = 0.93 and 0.90, respectively).[19]

The absolute difference in CAC score between MESA exam 2 and exam 5 was used as our primary endpoint, representing change in CAC over an average of 8 years. By design, only 50% of the MESA sample underwent CT at Exam 2. For those who did not undergo CT at exam 2, interpolated CAC was derived by averaging CAC of exam 1 and 3 assuming linear rate of change in CAC. Since approximately half of the participants who underwent exam 1 CT were randomly allocated to have a follow up CT at either exam 2 or 3 but not both, there was no overlap between the cohorts who underwent CT at exam 2 and 3. Notably, only one quarter of the full MESA cohort underwent CAC scans at exam 4 (September 2005 – May 2007); to maximize the size of cohort and the time interval over which CAC progression might occur, exam 5 CAC was chosen for calculating CAC change instead of exam 4 CAC.

Covariates

Information on demographics, smoking, physical activity, and medical conditions were obtained by questionnaire at exam 2. Smoking status was categorized as never, former, or current smoker. Physical activity was determined by calculation of weekly meter-minute

of total walking, conditioning and sports activity. Body mass index (BMI) obtained at exam 2 were categorized into normal (BMI <25 kg/m^2), overweight (25≤ BMI <30 kg/m^2) and obese (BMI ≥ 30 kg/m^2). Use of diabetes, hypertension and cholesterol medications was determined by questionnaire, and from medication containers which were brought to the exam 2 clinic visit. Blood samples collected after a 12 h fast were used to determine fasting glucose level, low (LDL) and high density lipoprotein-(HDL) cholesterol. Diabetes was defined as a fasting glucose ≥7.0 mmol/l (126 mg/dl), or use of insulin or oral hypoglycemic medications. Hypertension was determined by the sixth report of the Joint National Committee (1997) criteria.

Statistical analysis

Characteristics of participants were compared based on the self-reported sleep breathing history, the main exposure predictor of interest (i.e. No snoring, Snoring and OSA), using chi-square test or one way analysis of variance for categorical and continuous variables, respectively. Mean (standard deviation; SD) and percentage were used to describe continuous and categorical variables, as appropriate.

Absolute CAC score and prevalence for CAC (CAC score >0, i.e. presence of CAC) and CAC 400 (CAC score> 400, i.e. high burden of CAC) in the final cohort at baseline were calculated according to sleep breathing history characteristics using Kruskal Wallis test (with pair-wise post-hoc Wilcoxon test) and chi-square test respectively.

For multivariate comparison of the prevalence rate, Log binomial regression with a Poisson distribution was employed, with adjustment using the following nested models.

Model 1: age, gender race/ethnicity, education level, site, smoking and physical activity;

Model 2: Model 1 + BMI category; Model 3: Model 2 + several potential mediators of the association between OSA and CAC change (i.e. prevalent diabetes, prevalent hypertension, antihypertensive medication, HDL-C, LDL-C and lipid lowering medication).

The main outcome of interest, absolute CAC change was determined by subtracting CAC score at exam 2 (measured or interpolated) from that at exam 5. Multiple linear regression was performed to calculate the mean CAC change (and 95% confidence intervals) between the sleep breathing groups. The same models were employed as for the baseline prevalence comparison. Since there are several different approaches to analyzing change[20] , as a sensitivity analysis we modeled change with absolute CAC at exam 5 as the dependent variable, without considering baseline CAC values. Possible effect modification of associations between sleep breathing pattern and CAC change by age, gender, race, BMI category and reported excessive daytime sleepiness were tested by including cross-product terms in the models. A p-value less than 0.05 was considered significant. Sensitivity analysis was also performed after censoring participants with negative CAC change, which may represent measurement error. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, N.C.).

Results

A total of 2,603 participants were eligible for the main analysis evaluating change in CAC score between exam 2 and 5. This final cohort included 102 (3.9%) participants with OSA, 666 (25.6 %) with habitual snoring, and 1835 (70.5 %) without a history of

habitual snoring or OSA, who were therefore considered ‘normal’. This distribution was similar to the parent cohort [n=4,919, OSA: n = 3464 (3.9 %), Habitual snoring: n = 1261 (25.6 %), Normal: n = 194 (70.4 %)]. The baseline characteristics are shown in Table 1. Participants with OSA, when compared to those without OSA, were more likely to be male, obese and characterized by a higher prevalence of current smoking, diabetes, hypertension and being on medication for hypertension and hyperlipidemia. Levels of both HDL and LDL were lower among the OSA group; however after restricting the analysis to participants not taking lipid lowering medications, LDL levels were similar across sleep breathing categories. Overall, characteristics of the habitual snoring group were similar to those of the normal group. More than a third of participants with OSA (38.6%) reported having excessive daytime sleepiness compared to 27.9% and 18.5% in the habitual snoring and normal groups, respectively ($p < 0.0001$). Unadjusted baseline CAC score and CAC prevalence were significantly different across the groups (Table 1).

1. Prevalence of CAC at baseline from parent cohort (n =4919)

At baseline, the overall prevalence of positive CAC (CAC> 0) was high in all groups, but was highest in the OSA group (OSA: 64.4%; Habitual snoring: 55.0%; Normal: 55.6%, $p = 0.04$). Prevalence of high CAC burden (CAC> 400) showed similar pattern (OSA: 19.1%, Habitual snore: 10.4%, Normal: 12.0%, $p = 0.002$). In multivariate analyses, for CAC>0 the association was no longer present when adjusted for BMI (Table 2a). For CAC>400 the association persisted after adjustment for BMI and CVD risk factors (Table

2b). For both CAC>0 and CAC>400, the habitual snoring group behaved similarly to the normal group.

2. Longitudinal change in CAC (n = 2603)

Over 8 years of follow-up, CAC change in the final cohort ranged from -362 to 3261 and its mean and median were 140.4 and 25.9, respectively. Unadjusted change in CAC was significantly more pronounced in the OSA group compared to normal or habitual snoring groups [OSA: 227.7 (95% CI: 173.3-282.1); Habitual snoring: 140.4 (95% CI: 119.1-161.6), Normal: 135.6 (95% CI: 122.8-148.4)]. The pattern persisted in multivariate analysis adjusting for baseline demographic, life style factors [Model 1, OSA: 220.6 (95% CI: 169.2-272.0); Habitual snoring: 138.9 (95% CI: 118.5-159.3), Normal: 132.3 (95% CI: 120.1-144.4)] and BMI [Model 2, OSA: 204.2 (95% CI: 152.8-255.5); Habitual snoring: 132.6 (95% CI: 112.2-153.0), Normal: 135.5 (95% CI: 123.3-147.6)]. Figure 2 shows CAC scores at visit 2 and at visit 5, stratified by sleep breathing category, with model 2 adjustments. With further adjustment for CVD risk factors (model 3) the association between OSA and the normal group became statistically insignificant ($p = 0.08$), while the association remained significant in the between OSA and the habitual snoring group ($p = 0.04$). In sensitivity analyses modeling CAC at exam 5 (the follow up CAC) without taking into account baseline CAC, the results were slightly attenuated (Supplemental table 1).

Effect modification was not present by age, gender, BMI category or excessive daytime sleepiness but was present by race. Subsequent stratified analysis showed that in blacks,

no difference in CAC change was observed across the groups. This result should be viewed cautiously, however, given the number of comparisons and the limited sample size for race specific analyses.

In alternative analyses, when the OSA group was compared to combined 'no OSA group' (Habitual snoring + Normal group), the difference remained significant in model 1-2 but became marginally insignificant in model 3 adjusting for CVD risk factors ($p = 0.06$) (Supplemental table 2). Since negative change in CAC might be due to measurement error rather than a true regression, we performed analysis by excluding subjects (6%) with any negative change. The results were similar before and after the exclusion (data not shown). Finally because CAC change did not exhibit normally distributed pattern owing to large portion of cohort without significant change, we also performed the analysis using log-transformed CAC change. However results were largely unchanged (data not shown).

Discussion

In this large racially and ethnically diverse cohort without evidence of CVD at baseline, we found that having OSA based on self-reported physician diagnosis versus being a habitual snorer or reporting a normal sleep breathing pattern was associated with a significantly greater progression of CAC, as measured by absolute change in CAC scores over an average of 8 years. These associations remained significant even after adjusting for BMI, but were modestly attenuated after additionally accounting for key CVD risk factors, such as hypertension, diabetes and hyperlipidemia, which may be mediators of

the association between OSA and CAC progression. OSA has been linked to the development of these cardiovascular risk factors,[21,22] and these risk factors have been associated with CAC incidence and progression.[23]

Relatively few cross-sectional studies have explored the association between OSA and CAC prevalence, and they have yielded conflicting results, in both clinical and population based settings. One clinic based study of patients who were referred for both a sleep study and coronary CT showed a significantly higher prevalence of positive CAC and a higher CAC score in patients with OSA in a dose dependent manner according to the severity.[14] Such a finding however was not replicated in a similarly designed clinic based study.[13] One population based study showed an independent linear association of OSA severity with CAC score in women of all ages and in men less than 65 years old.[12] To the contrary, other studies involving a community cohort failed to show a significant independent association between OSA and prevalence or burden of CAC after adjusting for BMI.[11,15] Likewise, in the present study, the association between OSA and presence of CAC at baseline was not significant after adjusting for BMI. When CAC above 400 was considered, the association did persist after accounting for BMI, as well as traditional CVD risk factors.

A major advantage of our analysis over prior work is the prospective design, assessing the relation of OSA and CAC change over 8 years of follow-up. While baseline CAC score offers independent incremental information over and above traditional risk factors in the prediction of all-cause mortality,[24] progression of CAC has been shown to further increase the risk for coronary heart disease events in the MESA cohort.[25] Also within

MESA, self-reported OSA was found to be predictive of increased risk of incident CVD events and all-cause mortality.[26] Since OSA is considered a treatable condition, this provides an important basis for future studies evaluating the treatment of OSA on the development and progression of cardiovascular risk factors which may mediate the association between OSA and CAC progression.

Given that people who habitually snore are more likely to have undiagnosed OSA,[4] and the body of evidence relating habitual snoring to subclinical atherosclerosis and cardiovascular morbidities,[5-7] we hypothesized that those reporting 'habitual snoring' would have greater CAC progression than those reporting a normal sleep breathing pattern. However our analysis showed that, overall, CAC progression in the habitual snoring group was similar to that of the normal group. While this result suggests no significant association of habitual snoring with CAC progression, it may have been partly attributed to lack of validity of self-reported snoring history by participants possibly coupled with limitations of the survey to effectively separate the true "habitual" snorers from non-habitual snorers.[27] Thus, in future studies it would be valuable to explore CAC progression using an objective measurement of snoring (e.g. Audiotape recording or standard sleep study).

Although the underlying mechanism of OSA's effect on CAC progression is uncertain, it likely acts through repetitive airway obstruction and hypoxemia resulting in endothelial dysfunction[28] and inflammation[29,30] via oxidative stress[31] or heightened sympathetic activity[32]. Through these mechanisms, OSA may exert its deleterious effect on the progression of subclinical atherosclerosis either directly or indirectly via mediators such

as hypertension[33], diabetes[34] and metabolic syndrome,[35] which can all lead to hard CVD events such as coronary heart disease, stroke and heart failure as shown in recent prospective studies.[3,36]

Key strengths of this study are the prospective design which included an average of 8 years of follow-up, objectively measured CAC, and diverse study sample. A limitation of our study is the relatively small number of participants with OSA, which at times resulted in wide confidence intervals and perhaps imprecise estimates. OSA is known to be highly underdiagnosed in the community, particularly as many individuals with OSA lack classical symptoms.[37] Since in our sample diagnosis of OSA relied solely on self-reported history but not on the objective measurement, the prevalence of OSA (4%) reported in our study is almost certainly an underestimate. The subsequent misclassification would have likely biased our results toward the null. Bias related to unmeasured confounders in our hypothesized casual model or residual confounding resulting from inaccurate information of covariates should be also considered. In addition it is possible that a number of participants in the OSA group may have been receiving treatment for OSA, which may have weakened the association, though to date there is no supporting evidence of a beneficial effect of therapy on the progression of CAC. However, a graded relationship has been noted between adherence to OSA treatment using continuous positive airway pressure and total mortality.[38] Conversely, one can assume that participants with OSA in our study represent more symptomatic individuals who have more severe OSA, as they underwent a sleep study and received a diagnosis of OSA.

In addition, several caveats need to be explained in regards to the methodology of quantifying and analyzing CAC progression in our study. First we observed negative CAC change in varying degrees in a small number of subjects (6% of the final cohort). This likely represents measurement error, though true regression of coronary calcification is not impossible. Analysis removing participants with negative CAC progression did not change the results. Second, the absolute CAC score used to measure progression in our study can introduce an overestimation of the actual progression of CAC in subjects with higher baseline CAC as compared with those with low baseline CAC due to higher interscan variability.[39] Accordingly, given higher baseline CAC burden found in OSA group, we repeated the analysis adjusting for the baseline CAC score. The overall results were similar. Third, to enhance power, interpolated data based on an assumption of linear progression was used to estimate baseline CAC in approximately half of the cohort (those who had CAC measurement at Exams 1 and 3, but not Exam 2). Since our focus was on the absolute CAC change rather than an incidence of CAC, we believe interpolation was an acceptable approach.

In summary, in this large and racially/ethnically diverse cohort participants who self-reported physician diagnosis of OSA experienced greater CAC progression over 8 years of follow-up, relative to those who were habitual snorers or reported a normal sleep breathing pattern. Attenuation of the association after adjusting for important CVD risk factors suggests that these factors may mediate the association between OSA and CAC progression. CAC progression was similar among participants who reported habitual

snoring and those classified as normal. Our finding that participants with OSA experienced greater CAC progression provides an important rationale for further studies focusing on the effect of objectively measured OSA on the development of cardiovascular risk factors and subclinical cardiovascular disease.

[Tables]

Table 1. Characteristics of the participants in final cohort by self-reported sleep breathing history (n = 2603): MESA.

Variables	Normal (n = 1835)	Habitual Snoring (n= 666)	OSA (n=102)	p value
Demographics				
Age (years), mean (SD) [range]	61.8[a] (9.4) [46-86]	59.6[b] (8.6) [46-83]	59.5[b] (8.6) [46-81]	<.0001
Male n (%)	796 (43.4)	401 (60.2)	76 (74.5)	<.0001
Race n (%)				0.002
White, Caucasian	739 (40.3)	234 (35.1)	48 (47.1)	
Chinese American	203 (11.1)	97 (14.6)	7 (6.9)	
Black, African-American	504 (27.5)	162 (24.3)	30 (29.4)	
Hispanic	389 (21.2)	173 (26.0)	17 (16.7)	
Education, n (%)				0.0499
< High school degree	226 (12.3)	100 (15.0)	6 (5.9)	
High school degree or some college	883 (48.2)	300 (45.1)	47 (46.1)	
College graduate	725 (39.5)	265 (39.9)	49 (48.0)	
Income, n (%)				0.003
< $20000	328 (18.5)	112 (17.3)	8 (8.0)	
$20000 – 50000	679 (38.3)	233 (36.0)	30 (30.0)	
> $50000	767 (43.2)	302 (46.7)	62 (62.0)	
Life style				
Smoking n (%)				0.09
Never	889 (48.7)	288 (43.7)	39 (38.6)	
Former	754 (41.3)	295 (44.8)	49 (48.5)	
Current	184 (10.1)	76 (11.5)	13 (12.9)	
Physiologic Characteristics				
BMI category (kg/m^2), n (%)				<.0001
< 25	530 (28.9)	137 (20.6)	9 (8.8)	
25 – 30	775 (42.3)	254 (38.1)	36 (35.3)	
≥ 30	529 (28.8)	275 (41.3)	57 (55.9)	

Comorbidities				
Prevalent diabetes, n (%)	209 (11.5)	101 (15.3)	21 (20.8)	0.002
Prevalent HTN, n (%)	737 (40.6)	285 (43.3)	48 (47.5)	0.2
Hypertension medication, n (%)	655 (37.3)	270 (42.7)	47 (47.5)	0.01
HDL cholesterol (mg/dL) mean (SD) [range]	52.9[a] (15.2) [21-161]	48.0[b] (12.4) [24-111]	46.8[b] (10.5) [24-77]	<.0001
LDL cholesterol (mg/dL) mean (SD) [range]	113.0[a] (31.0) [21-243]	117.0[b] (30.3) [41-281]	104.3[c] (30.1) [34-178]	<.0001
Lipid Lowering meds, n (%)	380 (21.7)	75 (20.9)	31 (31.3)	0.07
Baseline CAC				
CAC score mean* (median) [range]	108.5[a] (0) [0-4744.1]	108.6[a] (1.2) [0-2963.9]	163.2[b] (19.3) [0-1175.5]	0.0006
Prevalence CAC > 0, n (%)	900 (49.1)	347 (52.1)	66 (64.7)	0.005
Prevalence CAC > 400, n (%)	132 (7.2)	48 (7.2)	17 (16.7)	0.002

CAC: coronary artery calcium; OSA: obstructive sleep apnea. For continuous variables, values without sharing common alphabet letters denote significant difference. * Kruskal Wallis test with pair-wise post-hoc Wilcoxon test was used.

Table 2. Prevalence ratio of positive CAC (Table 3a: CAC>0, Table 3b: CAC>400) at baseline in parent cohort by sleep breathing history (n=4919): MESA .

2a (CAC>0)

	Habitual snoring vs. Normal			OSA vs. Habitual snoring			OSA vs. Normal		
	PR	95% CI	p value	PR	95% CI	p value	PR	95% CI	p value
Model 1	1.05	0.99-1.11	0.1	1.11	1.00-1.23	0.05	1.16	1.06-1.29	0.002
Model 2	1.02	0.96-1.08	0.6	1.07	0.96-1.19	0.2	1.08	0.98-1.20	0.1
Model 3	1.03	0.97-1.08	0.4	1.03	0.92-1.15	0.7	1.05	0.95-1.17	0.4

2b (CAC> 400)

	Habitual snoring vs. Normal			OSA vs. Habitual snoring			OSA vs. Normal		
	PR	95% CI	p value	PR	95% CI	p value	PR	95% CI	p value
Model 1	1.09	0.90-1.31	0.4	1.51	1.11-2.06	0.009	1.64	1.24-2.17	0.0005
Model 2	1.02	0.84-1.24	0.8	1.38	1.01-1.88	0.04	1.41	1.06-1.87	0.02
Model 3	1.05	0.87-1.27	0.6	1.30	0.95-1.77	0.1	1.36	1.02-1.80	0.03

Model 1 adjusted for age, race, gender, site, income level, educational level, smoking status and physical activity level (n = 4703). Model 2 adjusted for Model 2 + BMI category (4702). Model 3 adjusted for Model 2 + Diabetes, Hypertension, Hypertension medication, LDL, HDL and Cholesterol medication (4401). CAC: coronary artery calcium; OSA: obstructive sleep apnea; PR: prevalence ratio.

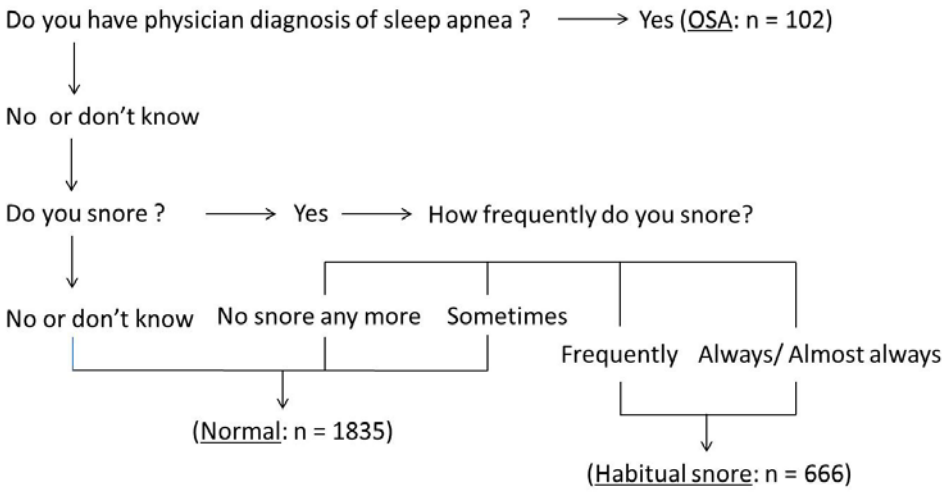
Table 3. Comparison of absolute CAC score change over 8 years of follow-up by sleep breathing history in the final analytic cohort (n= 2603): MESA.

	Normal (n = 1835)		Habitual snoring (n= 666)		OSA (n=102)		Habitual snoring vs. Normal	OSA vs. Habitual snoring	OSA vs. Normal
	Mean	95% CI	Mean	95% CI	Mean	95% CI		P value	
Model 1	132.3	120.1-144.4	138.9	118.5-159.3	220.6	169.2-272.0	0.6	0.004	0.001
Model 2	135.5	123.3-147.6	132.6	112.2-153.0	204.2	152.8-255.5	0.8	0.01	0.01
Model 3	138.2	126.2-150.3	129.7	109.3-150.2	185.9	134.8-236.9	0.5	0.04	0.08

Model 1 adjusted for age, race, gender, site, income level, educational, smoking status and physical activity level (n = 2502). Model 2 adjusted for Model 1 + BMI category (n= 2501). Model 3 adjusted for Model 2 + Diabetes, Hypertension, Hypertension medication, LDL, HDL and Cholesterol medication (n= 2344).
CAC: coronary artery calcium, OSA: obstructive sleep apnea.

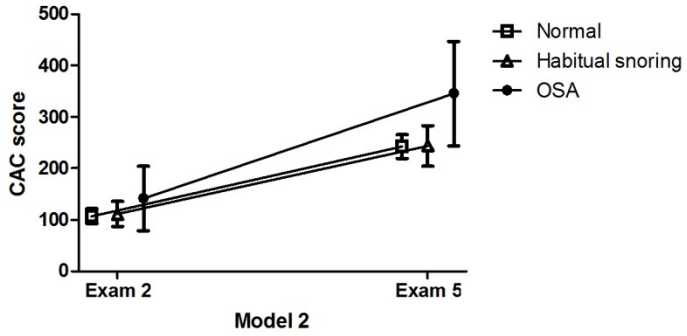
[Figures]

Figure 1. Construction of three sleep breathing history groups based on the self-administered sleep history questionnaire in final cohort (n = 2603): MESA



Snoring frequency response definitions: Sometimes: snoring up to 2 nights a week; Frequently: snoring 3-5 nights a week; Always or almost always: snoring 6-7 nights a week. Participants who responded either "No" or "don't know" to the question (a) but responded "Yes" to the snoring question (b) and "don't know" to the snoring frequency question (c) were also classified as normal. OSA: obstructive sleep apnea.

Figure 2. Adjusted* absolute CAC scores and CAC progression over 8 year period stratified by sleep breathing history: MESA



Mean and 95% CI of CAC score at exam 2 and 5 by sleep breathing history. *Model 2 adjusted for age, race, gender, site, income level, educational, smoking status, physical activity level and BMI category (n= 2501). P values comparing CAC change between the groups. Model 2: OSA vs. Normal: 0.01; OSA vs. Habitual snoring: 0.01; Habitual snoring vs. Normal: 0.8. CAC: coronary artery calcium, OSA: obstructive sleep apnea

[Supplemental Tables]

Supplemental Table 1. Absolute CAC score at exam 5 without accounting for baseline CAC values by self-reported sleep breathing category: MESA (Using **final cohort**; n = 2603)

	Normal (n = 1835)		Habitual snoring (n= 666)		OSA (n=102)		Habitual snoring vs. Normal	OSA vs. Habitual snoring	OSA vs. Normal
	Mean	95% CI	Mean	95% CI	Mean	95% CI		P value	
Model 1	238.5	214.9-262.1	251.7	212.2-291.3	365.6	265.9-465.3	0.6	0.04	0.02
Model 2	242.5	218.9-266.1	243.9	204.2-283.5	345.5	245.5-445.5	1.0	0.06	0.051
Model 3	249.6	225.5-273.7	243.3	202.4-284.2	311.9	209.7-414.1	0.8	0.8	0.2

Model 1 adjusted for age, race, gender, site, income level, educational, smoking status and physical activity level (n = 2502). Model 2 adjusted for Model 1 + BMI category (n= 2501). Model 3 adjusted for Model 2 + Diabetes, Hypertension, Hypertension medication, LDL, HDL and Cholesterol medication (n= 2344).
CAC: coronary artery calcium, OSA: obstructive sleep apnea.

Supplemental Table 2. Comparison of absolute CAC score change based on the presence of OSA in final cohort (n= 2603): MESA.

	No OSA n = 2501		OSA n = 102		
	Mean	CI	Mean	CI	p value
Model 1	134.0	123.7-144.4	220.3	169.0-271.7	0.001
Model 2	134.7	124.4-145.0	204.3	153.0-255.7	0.009
Model 3	136.0	125.8-146.2	186.4	135.4-237.4	0.06

Model 1 adjusted for age, race, gender, site, income level, educational, smoking status and physical activity level (n = 2502). Model 2 adjusted for Model 1 + BMI category (n= 2501). Model 3 adjusted for Model 2 + Diabetes, Hypertension, Hypertension medication, LDL, HDL and Cholesterol medication (n= 2344).
CAC: coronary artery calcium, OSA: obstructive sleep apnea.

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