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Associations Between Sleep Apnea and Subclinical Carotid Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis

Ying Y. Zhao, MD, MPH; Sogol Javaheri, MD; Rui Wang, PhD; Na Guo, MS; Brian B. Koo, MD; James H. Stein, MD; Claudia E. Korcarz, DVM; Susan Redline, MD, MPH

Background and Purpose—Many health effects of sleep apnea (SA) may be mediated through accelerated atherosclerosis. We examined the associations of snoring and several measurements of SA with subclinical carotid atherosclerosis in a large multiethnic population sample.

Methods—This analysis included 1615 participants (mean age, 68 years) from examination 5 (2010–2013) of the MESA study (Multi-Ethnic Study of Atherosclerosis). Sleep measures including SA (apnea-hypopnea index [4%], ≥15 events/hour) were derived from full in-home polysomnography. Carotid atherosclerosis was measured using high-resolution B-mode ultrasound. Multivariable linear and logistic regression models were used to evaluate the associations between sleep exposures with carotid intima-media thickness and the presence of carotid plaque, respectively. Effect modification by age, sex, and race/ethnicity was examined.

Results—In multivariable analysis, SA was associated with an increased odds of carotid plaque presence in individuals aged <68 years (odds ratio, 1.47; 95% CI, 1.05–2.06) but not in older individuals (odds ratio, 0.95; 95% CI, 0.67–1.37; *P* interaction=0.078). Greater hypoxemia (sleep time <90% saturation) was associated with increasing carotid intima-media thickness in younger (0.028±0.014 mm) but not in older individuals (−0.001±0.013 mm; *P* interaction=0.106). Self-reported snoring was not associated with carotid atherosclerosis. In assessing race-specific outcomes, greater hypoxemia was associated with increased carotid intima-media thickness in blacks (0.049±0.017 mm; *P* interaction=0.033).

Conclusions—In this large multiethnic population-based sample, sleep disturbances are associated with subclinical carotid atherosclerosis in both men and women, particularly in those <68 years of age. The mechanisms underlying the association between SA and carotid atherosclerosis may differ for carotid plaque and carotid intima-media thickness. **(*Stroke*. 2019;50:3340-3346. DOI: 10.1161/STROKEAHA.118.022184.)**

Key Words: aging ■ atherosclerosis ■ carotid intima-media thickness ■ sleep apnea ■ snoring

Stroke is a leading cause of disability, mortality, and economic burden in the United States.[1] Obstructive sleep apnea—a condition characterized by repetitive upper airway closure during sleep—affects an estimated 24% of men and 9% of women in the general population and may affect up to 50 to 70% of stroke patients.[1–3] There is a strong association between obstructive sleep apnea and increased risk of stroke[4–9]; however, associations may be stronger in men than in women.[4] The presence of obstructive sleep apnea is also associated with higher mortality and worse functional outcomes after stroke.[10]

Carotid intima-media thickness (CIMT) and carotid plaque are widely accepted noninvasive measures of atherosclerosis and subclinical arterial injury. Prior studies have demonstrated that CIMT and carotid plaque presence or burden are associated with increased incidence of cardiovascular events, including stroke, in individuals without history of cardiovascular disease (CVD).[11–17]

Several studies have demonstrated an association between sleep apnea (SA) and increased CIMT.[18] However, most of these previous studies were small and did not fully control for potential confounders and did not study an ethnically diverse sample. Furthermore, few studies have evaluated the relationship between SA and carotid plaque, which more recent studies have found to be a stronger predictor of incident CVD than CIMT.[19]

The objective of this study was to examine the association between snoring, SA, and subclinical carotid atherosclerosis

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Received August 22, 2018; final revision received August 16, 2019; accepted August 27, 2019.

From the Division of Sleep and Circadian Disorders, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (Y.Y.Z., S.J., R.W., N.G., S.R.); Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA (R.W.); Department of Neurology, Yale University, New Haven, CT (B.B.K.); School of Medicine and Public Health, University of Wisconsin, Madison (J.H.S., C.E.K.); and Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA (S.R.).

Guest Editor for this article was Emmanuel Touzé, PhD.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.118.022184.

Correspondence to Ying Y. Zhao, MD, Harvard Medical School, 221 Longwood Ave, Suite BL225, Boston, MA 02115. Email yingzhao@mail.harvard.edu

in a large multiethnic population sample and assess variations by age, sex, and race/ethnicity. Given stronger associations between CVD and SA in middle-aged compared with older individuals[20–22] and in men compared with women,[4] we hypothesized that the associations between subclinical atherosclerosis with SA would be stronger in younger individuals and in men, as compared with their counterparts.

Methods

Anonymized data and materials have been made publicly available at BioLINCC and can be accessed at https://biolincc.nhlbi.nih.gov/home/. Polysomnography data are available at the National Sleep Research Resource and can be accessed at https://sleepdata.org.

See the online-only Data Supplement for detailed Methods.

Study Population

MESA (Multi-Ethnic Study of Atherosclerosis) is a prospective study designed to investigate risk factors for incident CVD and progression of subclinical CVD in an ethnically diverse population.[23] Between July 2000 and August 2002, 6814 men and women aged 45 to 85 years and free of clinically apparent CVD were recruited from 6 US centers. At MESA Exam 5 (2010–2013), eligible participants were invited to participate in the MESA Sleep Study. The present cohort consists of 1615 participants with successful polysomnography and carotid ultrasound data at Exam 5. The study was approved by the institutional review board at each center, and written informed consent was obtained from all participants.

Polysomnography

Detailed MESA polysomnography methodology has been published.[24] Sleep stages and arousals were scored by the Brigham and Women's Hospital Sleep Reading Center according to published guidelines[25] adapted from the Sleep Heart Health Study.[26,27] Apneas were scored when the thermocouple signal flattened or nearly flattened for >10 seconds. Hypopneas were scored if there was a >30% reduction in amplitude of either respiratory effort or airflow for ≥10 seconds. SA was defined by an apnea-hypopnea index (AHI) ≥15 events/h (all apneas and hypopneas associated with ≥4% oxygen desaturation).

Carotid Ultrasonography

B-mode ultrasound images of the carotid artery were reviewed and interpreted by the University of Wisconsin Atherosclerosis Imaging Research Program MESA Carotid Ultrasound Reading Center.[28] The distal common carotid artery was defined as the distal 10 mm of the vessel. Intima-media thickness was defined as the intima-media thickness measured as the mean of the mean left and right mean far wall distal common carotid artery wall thicknesses. Carotid plaque score (0–12) was defined as the number of carotid plaques in the internal, bifurcation, and common segments of both carotid arteries. Carotid plaque was defined as a discrete, focal wall thickening ≥1.5 cm or focal thickening >50% greater than the surrounding intima-media thickness.[28]

Other Measures

Habitual snoring was considered if participants reported snoring sometimes (3–5 nights/wk) or always/almost always (6–7 nights/wk) on the sleep questionnaires.

Covariates

Race/ethnicity was self-identified as white, black, Hispanic, and Chinese.

Statistical Analyses

Data are reported as mean (SD) for continuous variables and percentages for categorical variables. Between-group comparisons were made using χ^2 tests, *t* tests, and Wilcoxon rank-sum tests for categorical, normally, and non-normally distributed continuous variables, respectively.

Linearity of dose-response relationship between AHI and mean common carotid artery was assessed by fitting a linear regression model using quartiles of AHI as a categorical variable and assessing linearity by graphical examination and by likelihood ratio testing.

Logistic regression models were used to assess the association between SA (AHI ≥15 events/h) and other sleep measures with the presence of carotid plaque, adjusting for age, race/ethnicity, and sex (model 1); further adjusting for body mass index and pack-years smoked (model 2) and additionally adjusting for factors that could be confounders or potentially in the causal pathway including alcohol use, the presence of hypertension and diabetes mellitus, serum total cholesterol and triglyceride level, and use of statin medications (model 3). Similarly, linear regression models were used to examine the association between SA and other sleep measures with mean CIMT. We also examined the relationship between sleep time with oxygen saturation <90% (Spo_2)—a non-normally distributed variable—and measures of carotid atherosclerosis, by analyzing sleep time with Sp_{o_2} <90% as a dichotomized variable (median of ≥0.64%). Since age, sex, and race/ethnicity may be important effect modifiers of the relationship between AHI and carotid atherosclerosis, we assessed whether the associations varied by age, sex, or race/ethnicity by adding interaction terms into the models with age dichotomized at the median of 68 years. Statistical analysis was performed using SAS, version 9.4 (Cary, NC).

Results

Baseline characteristics of the sample are shown in Table 1. The mean age (SD) of the cohort was 68.7 (9.1) years; 54.1% were women, and 64.5% were nonwhites. Moderate-to-severe SA (AHI ≥15) was present in 32.9% of participants. Participants with SA were more likely men, had higher body mass index, and greater CVD risk factors including hypertension and diabetes mellitus than those without SA. The mean (SD) CIMT was 0.86 mm (0.20), and 66.4% of participants had ≥1 carotid plaques with a median carotid plaque score of 1 (interquartile range, 0–4). Individuals with SA were more likely to have carotid plaque and higher CIMT than those without SA.

Participant characteristics by the presence of carotid plaque are shown in Table I in the online-only Data Supplement. Individuals with carotid plaque had higher AHI levels, more sleep hypoxemia, and more fragmented sleep as noted by lower sleep maintenance efficiency, higher arousal index, and more N1 and less rapid eye movement sleep.

Carotid Plaques

After adjusting for demographic factors, a positive but nonsignificant association between SA and carotid plaque was observed, which was attenuated after adjustment for body mass index and smoking with further attenuation after adjusting for multiple cardiovascular risk factors and medications (Table 2). A similar trend was observed for the association between arousal index and carotid plaque. In adjusted analyses, there was no evidence for significant associations between hypoxemia, sleep efficiency, sleep duration, or slow-wave sleep duration in the overall cohort.

Analysis that included the potential for moderation by age and adjusted for demographics, obesity, and smoking showed that SA was associated with a 51% increased odds of carotid plaque in individuals aged <68 years (odds

Table 1. Baseline Characteristics by the Presence of SA (SA: AHI ≥15 Events/h)

	Total Sample, n=1615	SA (AHI ≥15), n=531	No SA (AHI <15), n=1084	*P* Value
Age, y				
Mean±SD	68.7±9.1	69.1±8.9	68.4±9.2	0.108
Median [IQR]	68 [61–76]	69.0 [62–76]	68.0 [61–75]	
Men, n (%)	741 (45.9)	325 (61.2)	416 (38.4)	<0.0001
Race, n (%)				
White	573 (35.5)	170 (32.0)	403 (37.2)	0.003
Chinese	207 (12.8)	81 (15.3)	126 (11.6)	
Black	447 (27.7)	131 (24.7)	316 (29.2)	
Hispanic	388 (24.0)	149 (28.1)	239 (22.1)	
BMI, kg/m^2	28.6 (5.5)	30.5±5.7	27.7±5.1	<0.0001
Smoking status, n (%)				
Never	759 (47.2)	245 (46.3)	514 (47.6)	0.215
Former	740 (46.0)	255 (48.2)	485 (44.9)	
Current	110 (6.8)	29 (5.5)	81 (7.5)	
Pack-years smoked	0 (0–12.4)	0 (0–12.5)	0 (0–12.2)	0.620
Current alcohol use, n (%)	690 (42.9)	232 (43.9)	458 (42.4)	0.581
Lipid-lowering medication use, n (%)	612 (37.9)	221 (41.6)	391 (36.1)	0.031
Antihypertensive use, n (%)	873 (54.1)	314 (59.1)	559 (51.6)	0.004
Presence of hypertension, n (%)	973 (60.3)	344 (64.8)	629 (58.0)	0.009
Mean systolic blood pressure, mm Hg	123.1±20.3	124.2±19.4	122.5±20.7	0.063
Mean diastolic blood pressure, mm Hg	68.1±9.8	69.3±9.6	67.6±9.8	0.002
Presence of diabetes mellitus, n (%)	352 (22.1)	148 (28.1)	204 (19.1)	<0.0001
Serum total cholesterol, mg/dL	183.9±36.2	179.7±36.9	186.0 (35.7)	0.003
Serum low-density lipoprotein, mg/dL	106.4±32.0	104.4±32.8	107.4±31.6	0.156
Serum high-density lipoprotein, mg/dL	55.8±16.4	51.5±14.0	57.9±17.2	<0.0001
Serum triglyceride, mg/dL	110.0±61.8	120.5±69.3	104.8±57.1	<0.0001
HMG-CoA reductase (statin) use, n (%)	581 (36.0)	211 (39.7)	370 (34.1)	0.028
Self-reported snoring, n (%)				
None habitual snorer (1–2 nights/wk)	449 (28.0)	105 (19.8)	344 (32.0)	<0.0001
Habitual snorer (3–7 nights/wk)	644 (40.1)	270 (50.9)	374 (34.8)	
Unknown	512 (31.9)	155 (29.3)	357 (33.2)	
Carotid ultrasound measures				
Total carotid plaque score, median [IQR]	1 [0–4]	2.0 [0–4]	1.0 [0–3]	0.015
Presence of carotid plaque, n (%)	1073 (66.4)	373 (70.2)	700 (64.6)	0.023
Mean common CIMT, mm				
Mean±SD	0.86±0.20	0.88±0.19	0.85±0.20	0.001
Median [IQR]	0.82 [0.73–0.96]	0.84 [0.74–0.99]	0.82 [0.72–0.95]	
Polysomnography sleep measures				
Total sleep duration, min	360.8±81.8	350.0±83.4	366.3±80.5	0.0001
Sleep maintenance efficiency, %	79.7±12.6	76.6±13.3	81.3±11.9	<0.0001
Arousal index, events/h	22.0±11.9	29.6±13.9	18.3±8.7	<0.0001
Sleep time in stage 1 sleep, %	14.2±8.9	19.0±11.0	11.9±6.5	<0.0001
Sleep time in stage 2 sleep, %	57.6±10.1	56.4±10.6	58.2±9.7	0.008
Sleep time in slow-wave sleep (N3), %	10.2±9.0	8.3±8.0	11.1±9.2	<0.0001
Sleep time in REM sleep, %	18.1±6.7	16.3±7.1	18.9±6.3	<0.0001
Sleep time with Sp_{O_2} <90%, %; median	0.64 [0.1–3.1]	4.0 [1.6–9.4]	0.2 [0–1.0]	<0.0001
Average Sp_{O_2} in sleep, %; median [IQR]	94.8 [93.5–95.7]	93.8 [92.7–94.8]	95.0 [94.0–96.0]	<0.0001

Data are presented as number (%), mean±SD, or median [IQR]. *P* values for continuous data are from Wilcoxon rank-sum test. *P* values for categorical data are from a χ^2 test. AHI indicates apnea-hypopnea index; BMI, body mass index; CIMT, carotid intima-media thickness; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; IQR, interquartile range; REM, rapid eye movement; SA, sleep apnea; and Sp_{O_2}, oxygen saturation.

ratio, 1.51; 95% CI, 1.08–2.10) but not in older individuals (odds ratio, 1.02; 95% CI, 0.72–1.46; *P* interaction=0.105). The association persisted in the younger group after further adjusting for major cardiovascular risk factors (odds

Table 2. Association Between SA and Other Sleep Measures and the Presence of Carotid Plaque

	Model 1: OR (95% CI)	*P* Value	Model 2: OR (95% CI)	*P* Value	Model 3: R (95% CI)	*P* Value
SA (AHI ≥15 events/h)	1.26 (0.99–1.60)	0.056	1.22 (0.94–1.56)	0.130	1.16 (0.90–1.51)	0.250
Arousal index (events/h)	1.01 (1.00–1.02)	0.076	1.01 (1.00–1.02)	0.132	1.01 (1.00–1.02)	0.143
Sleep maintenance efficiency, %	1.00 (0.99–1.00)	0.329	1.00 (0.99–1.01)	0.402	1.00 (0.99–1.01)	0.497
≥0.64% sleep time with Sp_{o_2} <90%, %	1.13 (0.91–1.41)	0.254	1.04 (0.82–1.32)	0.723	1.02 (0.80–1.30)	0.873
Total sleep duration, min	1.00 (1.00–1.00)	0.521	1.00 (1.00–1.00)	0.671	1.00 (1.00–1.00)	0.768
Slow-wave sleep (N3), %	1.00 (0.99–1.02)	0.686	1.00 (0.99–1.02)	0.606	1.00 (0.99–1.02)	0.579

Model 1: adjusted for demographic factors (continuous age, race/ethnicity, and sex). Model 2: additionally adjusted for pack-years smoked and body mass index. Model 3: additionally adjusted for alcohol use, presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, and HMG-CoA reductase (statin) use. AHI indicates apnea-hypopnea index; OR, odds ratio; SA, sleep apnea; and Sp_{o_2}, oxygen saturation.

ratio, 1.47; 95% CI, 1.05–2.06), with no evidence of association in the older sample (*P* interaction=0.078; Table 3). Although the test for age interaction was not significant, there also appeared to be a positive association between increasing arousal index and carotid plaque in individuals aged <68 years, which was not observed in older individuals. Stronger associations between hypoxemia and carotid plaque were suggested in younger than older individuals in analyses adjusted for demographic factors; however, these associations were not significant in more fully adjusted models.

Carotid Intima-Media Thickness

In minimally adjusted models, greater hypoxemia (≥0.64% with Sp_{o_2} <90%) was associated with higher CIMT. However, in fully adjusted models, no significant association between SA or other sleep measures and CIMT was observed (Table 4). In age group–specified analysis adjusted for demographic factors, smoking, and body mass index, a significant association was observed between a higher percentage of sleep time with Sp_{o_2} <90% and CIMT in the younger (β±SE, 0.032±0.014 mm) but not older participants (0.001±0.013 mm); *P* interaction=0.089 (Table 5). This association was slightly attenuated after additionally adjusting for additional cardiovascular risk factors.

Analyses evaluating effect modification by sex did not identify significant sex differences although the association between SA and carotid plaque tended to be stronger in men than in women (online-only Data Supplement). Associations between carotid plaque and SA were stronger in whites than in other racial/ethnic groups. In fully adjusted analyses, significant associations were demonstrated between greater hypoxemia and CIMT in blacks but not in other groups (*P* interaction=0.033). Higher sleep efficiency was associated with CIMT in Hispanics.

Discussion

In this large ethnically/racially diverse community sample, we identified no significant associations between indices of carotid atherosclerosis with measures of disturbed sleep in the overall cohort although several significant associations were observed in individuals and in race-specific analyses. Our results highlight several important findings. First, SA was associated with carotid plaque in individuals <68 years of age. Higher arousal index also showed a similar pattern of association with carotid plaque in the younger cohort members. Second, decreased oxygen saturation during sleep was the only sleep measure associated with an increase in CIMT but only in younger or black individuals. Third, there was no association between self-reported habitual snoring and

Table 3. Association Between SA and Other Sleep Measures and the Presence of Carotid Plaque by Dichotomized Age

	Model 1: OR (95% CI), *P* Value	*P* Interaction	Model 2: OR (95% CI), *P* Value	*P* Interaction	Model 3: OR (95% CI), *P* Value	*P* Interaction
SA (AHI ≥15 events/h)						
Age <68 y	1.56 (1.14–2.13), 0.006	0.064	1.51 (1.08–2.10), 0.015	0.105	1.47 (1.05–2.06), 0.027	0.078
Age ≥68 y	1.01 (0.71–1.42), 0.968	0.064	1.02 (0.72–1.46), 0.892	0.105	0.95 (0.67–1.37), 0.798	0.078
Arousal index (events/h)						
Age <68 y	1.02 (1.00–1.03), 0.020	0.252	1.02 (1.00–1.03), 0.020	0.404	1.01 (1.00–1.03), 0.035	0.264
Age ≥68 y	1.00 (0.99–1.02), 0.577	0.252	1.00 (0.99–1.02), 0.577	0.404	1.00 (0.99–1.02), 0.664	0.264
≥0.64% sleep time with Sp_{o_2} <90%, %						
Age <68 y	1.37 (1.03–1.82), 0.033	0.086	1.29 (0.95–1.75), 0.108	0.119	1.25 (0.91–1.71), 0.166	0.127
Age ≥68 y	0.94 (0.68–1.29), 0.688	0.086	0.91 (0.65–1.27), 0.568	0.119	0.88 (0.63–1.24), 0.463	0.127

Model 1: adjusted for demographic factors (dichotomized age, race/ethnicity, and sex) and interaction term between age and sleep parameter. Model 2: additionally adjusted for pack-years smoked and body mass index. Model 3: additionally adjusted for alcohol use, the presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, HMG-CoA reductase (statin) use. AHI indicates apnea-hypopnea index; OR, odds ratio; SA, sleep apnea; and Sp_{o_2}, oxygen saturation.

Table 4. Association Between SA and Other Sleep Measures and Carotid Intima-Media Thickness

	Model 1: β±SE	*P* Value	Model 2: β±SE	*P* Value	Model 3: β±SE	*P* Value
SA (AHI ≥15 events/h)	0.011±0.010	0.264	−0.002±0.010	0.807	−0.005±0.010	0.642
Arousal index (events/h)	0.0004±0.0004	0.332	0.0001±0.0004	0.793	0.00004±0.0004	0.918
Sleep maintenance efficiency, %	−0.0003±0.0004	0.361	−0.00008±0.0004	0.835	0.000004±0.0004	0.992
≥0.64% sleep time with Sp_{0_2} <90%, %	0.021±0.009	0.018	0.009±0.009	0.346	0.007±0.010	0.444
Total sleep duration, min	−0.00004±0.0001	0.478	0.00000±0.0001	0.997	0.000005±0.0001	0.923
Slow-wave sleep, (N3) %	−0.0007±0.0005	0.197	−0.0005±0.0005	0.340	−0.0006±0.0005	0.279

Model 1: adjusted for demographic factors (continuous age, race/ethnicity, and sex). Model 2: additionally adjusted for pack-years smoked and body mass index. Model 3: additionally adjusted for alcohol use, the presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, and HMG-CoA reductase (statin) use. AHI indicates apnea-hypopnea index; SA, sleep apnea; and Sp_{0_2}, oxygen saturation.

either measure of carotid atherosclerosis. Fourth, sex did not appear to significantly modify the observed associations. Our findings suggest that (1) increase in carotid plaque and intima-media thickness may reflect different sleep related stressors. Specifically, carotid plaque may result from the adverse effects of recurrent respiratory disturbances and possible arousal-related sympathetic surges, while CIMT may be increased secondary to stressors associated with hypoxemia, such as inflammation, endothelial dysfunction, hypertension, and dyslipidemia[29]; (2) associations between sleep disturbances and carotid atherosclerosis tend to be stronger in individuals <68 years of age compared with older individuals and in blacks compared with other race/ethnicities although the associations do not vary by sex.

Several epidemiological studies have reported an increased prevalence or incidence of cardiovascular and cerebrovascular disease in individuals with SA.[30] The available data, however, raise questions regarding the impact of alternative sleep exposures on risk, as well as suggest heterogeneity in susceptibility to vascular disease across population groups. Although a meta-analysis of published studies reported higher CIMT in patients with obstructive sleep apnea (pooled standardized difference in means, 1.40 [lower limit, 0.996, to upper limit, 1.803]),[18] the authors emphasized limitations of the available data; most studies included <100 subjects, have a high degree of bias and heterogeneity, and many did not comprehensively adjust for confounders.

The present study is the largest cohort study to date to examine the association between SA and subclinical carotid atherosclerosis and the first to evaluate the influences of age, sex, and race/ethnicity on this association using rigorously collected sleep measures in a large multiethnic cohort. After adjusting for potential confounders, we observed an association between SA and carotid plaque only among the younger cohort members. We also observed a significant association between CIMT and decreased oxygen saturation during sleep in the younger cohort. These results are consistent with results of the Wisconsin Sleep Study, which found that among individuals with a mean baseline age of 47 years, AHI predicted future carotid plaque presence and score but not CIMT.[31] A subsequent study by the same authors found that minimum oxygen saturation, but not other measures of hypoxemia, predicted development of carotid plaques.[32] However, minimal oxygen saturation does not fully capture hypoxic burden associated with SA. Our analyses also suggest an association of increasing arousal index and carotid plaque in the younger individuals, which is consistent with a prior study from MESA showing that a higher arousal index was associated with high coronary artery calcium scores.[33] The underlying mechanism may be arousal-associated sympathetic activity and blood

Table 5. Association Between SA and Other Sleep Measures and Carotid Intima-Media Thickness by Dichotomized Age

	Model 1: β±SE, *P* Value	*P* Interaction	Model 2: β±SE, *P* Value	*P* Interaction	Model 3: β±SE, *P* Value	*P* Interaction
SA (AHI ≥15 events/h)		0.041		0.058		0.072
Age <68 y	0.034±0.014, 0.018		0.022±0.015, 0.125		0.019±0.015, 0.200	
Age ≥68 y	−0.006±0.014, 0.658		−0.014±0.014, 0.299		−0.016±0.014, 0.242	
Arousal index (events/h)		0.389		0.641		0.499
Age <68 y	0.0009±0.0006, 0.115		0.0006±0.0006, 0.335		0.0005±0.0006, 0.341	
Age ≥68 y	0.0002±0.0005, 0.688		0.0002±0.0005, 0.724		0.00002±0.0005, 0.969	
≥0.64% sleep time with Spo2 <90%, %		0.045		0.089		0.106
Age <68 y	0.042±0.013, 0.001		0.032±0.01, 0.021		0.028±0.014, 0.038	
Age ≥68 y	0.006±0.013, 0.664		0.0007±0.013, 0.955		−0.001±0.013, 0.928	

Model 1: adjusted for demographic factors (dichotomized age, race/ethnicity, and sex) and interaction term between age and sleep parameter. Model 2: additionally adjusted for pack-years smoked and body mass index. Model 3: additionally adjusted for alcohol use, the presence of hypertension and diabetes mellitus, serum total cholesterol, serum triglyceride level, and HMG-CoA reductase (statin) use. AHI indicates apnea-hypopnea index; SA, sleep apnea; and Sp_{0_2}, oxygen saturation.

pressure surges.[30] Interestingly, adjustment for hypertension (and other potential intermediate mechanisms) did not substantively alter the odds ratio for this association. However, daytime blood pressure may not reflect the nocturnal blood pressure surges that accompany arousals.

Significant age interaction was previously described between SA and measures of CVD and risk factors. In the Sleep Heart Health Study, SA was associated with systolic/diastolic hypertension in those aged <60 years but not older individuals.[21] A higher incidence of coronary heart disease in association with SA was also reported in younger compared with older individuals.[20] In MESA, left ventricular mass was associated with AHI in the younger cohort members.[22] An association between SA and markers of inflammation was also found to be stronger in younger members of MESA.[34] The reasons for the observed effect modification by age are not well understood. Possible explanations include age variation in SA characteristics influencing susceptibility to carotid atherosclerosis such as decreased intrathoracic pressure generated with apneic events and altered chemoreflex and autonomic responses to ventilatory disturbances in older individuals. It is also possible that the weaker associations in older individuals reflect survival bias. Overall, the findings of stronger association between SA and carotid atherosclerosis in younger individuals provide support for the potential benefit of early diagnosis and treatment of SA in preventing CVD.

An unexpected finding was the positive association between sleep efficiency and CIMT in Hispanic individuals. Although this may have been spurious, it is possible that this association may reflect the greater propensity of individuals with a high sleep drive to develop CVD, as suggested by evidence that sleepiness identifies individuals with SA at risk for CVD.[35]

Although carotid plaque and CIMT are both markers of carotid atherosclerosis, our study points to different associations between indices of disturbed sleep and each measure. These findings are supported by prior data showing CIMT and plaques to reflect different stages and aspects of atherosclerosis, representing different adaptive responses to traditional cardiovascular risk.[15] More recent studies show that carotid plaque presence and carotid plaque score are stronger predictors of CVD and cerebrovascular events than CIMT.[15,16,18,36]

Strengths of our study include the use of a community-based sample of ethnically diverse women and men. Standardized polysomnography measures and carotid ultrasound reading reduced measurement error, reporting biases, and increased precision. Study limitations include the cross-sectional design, such that one cannot infer causality. The study may be underpowered to detect subgroup interactions. Additional studies powered to evaluate age and race/ethnicity interaction will be of particular interest to further explore the observed association between deceased oxygen saturation during sleep and increased CIMT in blacks. The use of plaque presence may have less predictive value than quantitative measures of plaques. Finally, despite adjustments for multiple potential confounders, we cannot exclude residual confounding.

In conclusion, our study findings indicate that sleep disturbances are associated with subclinical carotid atherosclerosis in men and women <68 years of age. Further, they suggest that the mechanisms underlying the association between SA and carotid atherosclerosis may differ for carotid plaque and CIMT—two biologically and genetically distinct forms of carotid atherosclerotic burden. Finally, race differences suggest the potential for an increased susceptibility of blacks to the effects of hypoxemia.

Acknowledgments

All authors contributed to the design, data interpretation, and manuscript preparation. All authors agree to be accountable for all aspects of the work.

Sources of Funding

This research was supported by contracts HHSN2682015000031, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute (NHLBI); grants UL1-TR-000040 and UL1-TR-001079 from the National Center for Research Resources (NCRR); and NHLBI grants HL098433, HL110350, K23 KL094760, HL113338, and R35HL135818.

Disclosures

None.

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