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Association of sleep apnea and sleep duration with peripheral artery disease: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background and aims—Numerous biological pathways linking sleep disturbances to atherosclerosis have been identified, such as insulin resistance, inflammation, hypertension, and endothelial dysfunction. Yet, the association of sleep apnea and sleep duration with peripheral artery disease (PAD) is not well characterized.

Methods—We evaluated the cross-sectional association between objectively measured sleep and prevalent PAD in 1,844 participants (mean age 68 years) who in 2010–2013 had in-home polysomnography, 7-day wrist actigraphy and ankle-brachial index (ABI) measurements. We also

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Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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evaluated the relation between self-reported diagnosed sleep apnea and PAD incidence in 5,365 participants followed from 2000 to 2012. PAD was defined as ABI<0.90.

Results—In cross-sectional analyses, severe sleep apnea [apnea-hypopnea index (AHI) ≥ 30 vs. AHI <5] was associated with greater prevalent PAD only among black participants [multivariate adjusted prevalence ratio (95% CI): 2.29 (1.07–4.89); p-interaction = 0.05]. Short and long sleep duration was also associated with a 2-fold higher prevalence of PAD as compared with those who slept 7h/night, in the full sample. In longitudinal analyses, participants with self-reported diagnosed sleep apnea were at higher risk of incident PAD [multivariable adjusted hazard ratio (95% CI): 1.93 (1.05–3.53)], with no evidence of interaction by race/ethnicity.

Conclusions—These findings support a significant association between sleep apnea and prevalent and incident PAD, with evidence for stronger associations with objectively measured sleep apnea and cross sectional PAD in blacks. In addition, short and long sleep duration was associated with PAD. These results identify sleep disturbances as a potential risk factor for PAD.

Keywords

epidemiology; obstructive sleep apnea; sleep duration; peripheral artery disease; longitudinal study; community-based study

Introduction

Sleep apnea is common in the US adult population; approximately 13% of men and 6% of women have moderate to severe sleep apnea[1]. The condition is characterized by repetitive episodes of breathing pauses, with resultant hypoxemia and sleep fragmentation. Short sleep duration also is highly prevalent in the population [2] and may lead to elevations in inflammatory cytokines[3] and blood pressure [4]. Over the past two decades, numerous studies have reported associations of sleep apnea and abnormal sleep duration (long and short) with CVD risk factors and events, independent of adiposity[5–7]. Numerous biological pathways linking sleep disturbances to atherosclerosis have been identified, such as insulin resistance, inflammation, hypertension, and endothelial dysfunction [8,9].

Peripheral artery disease (PAD) affects approximately 8.5 million Americans (7.2% of the population) aged 40 years or older[10] and is associated with significant morbidity and mortality, as well as reduced quality of life. However, the association of sleep apnea with PAD is not well characterized[11], and heretofore there have been no longitudinal studies examining this association. Similarly, although short and long sleep duration have also been associated with increased CVD risk factors[12] and subclinical atherosclerotic markers [e.g. intimal medial thickness and coronary artery calcium] [13], the association of abnormal sleep duration with PAD is not studied.

Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), we tested the hypotheses that a) objectively measured sleep apnea and short and long sleep durations are associated with greater PAD prevalence, and b) self-reported sleep apnea is associated with greater incidence of PAD, independent of other traditional CVD risk factors.

Materials and methods

Participants

The MESA[14] cohort includes 6,814 women and men aged 45–84 years old recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN) in 2000–2002. Participants self-identified as Caucasian (38%), non-Hispanic African American (28%), Hispanic (22%) or Chinese (12%). A total of 5 clinic examinations have now taken place (Exam 1: 2000–2002, Exam 2: 2002–2004, Exam 3: 2004–2005, Exam 4: 2005–2007, Exam 5: 2010–2013). The study timeline and data collection parameters key to the present analyses are summarized in Figure 1. Local institutional review boards approved study protocols, and all participants gave written informed consent.

Cross-sectional analyses

Participants—All 4,077 MESA participants who took part in Exam 5 received an initial invitation to participate in the sleep ancillary study. Those reporting regular use of oral devices, nocturnal oxygen, or nightly positive airway pressure (PAP) devices ($n = 147$) or who lived too far away ($n = 141$) were deemed ineligible[15]. Of the remaining 3,789 participants, 2,261 participated in the sleep exam (59.7%). As has been reported elsewhere[15], characteristics of participants who took part in the sleep study were similar to those of participants who did not, though participants were slightly more likely to be White, older, current/ex-smokers, and to have hypertension and chronic obstructive pulmonary disease. The sleep ancillary study included in-home overnight polysomnography (PSG), 7-day wrist actigraphy, and sleep questionnaires. Data that met quality metrics were obtained from 1,922 participants. For the present cross-sectional analysis, we excluded participants without data for ankle-brachial index (ABI) at Exam 5 ($N=40$), and those with an ABI >1.40 ($N=34$) or with incomplete data on key covariates ($N=4$). The final analytic sample included 1,844 participants (Supplemental Figure 1).

Exposures—An overnight unattended in-home polysomnogram was conducted following a standardized protocol using a 15-channel monitor, Compumedics Somte System (Compumedics Ltd., Abbotsville, Australia), as described elsewhere [15].

Sleep apnea was defined by the apnea-hypopnea index (AHI), which is the average number of apnea and hypopnea events per hour of sleep, and includes all apneas (regardless of desaturation or arousal) and hypopneas with $\geq 4\%$ oxygen desaturation. The inter- and intra-scorer intra-class correlation coefficients of AHI ranged from 0.95 to 0.99. Participants were categorized into four sleep apnea severity groups according to the AHI: <5.0 (normal), 5.0–14.9 (mild), 15.0–29.9 (moderate), and ≥ 30.0 (severe). Nocturnal hypoxemia and the arousal index were included in the analysis as secondary exposures; methods and definitions of these indices are provided in the Supplemental Methods.

Sleep duration was measured by wrist actigraphy measurements (Actiwatch Spectrum, Philips Respironics, Murrysville, PA). Participants were asked to wear the Actiwatch Spectrum (PA, USA) on the non-dominant wrist for seven consecutive days. Data were

scored in 30-second epochs as sleep or wake using Actiware-Sleep version 5.59 software as previously described [15]. Participants were categorized into four sleep duration groups: <6.0, 6.0–6.9, 7.0–7.9 (reference), and ≥ 8.0 hours.

Prevalent PAD—Systolic blood pressure measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position using a hand-held Doppler instrument with a 5-mHz probe. For each lower extremity, the ABI numerator used was the highest pressure (dorsalis pedis or posterior tibial) from that leg. The leg cuff was inflated to a maximum of 300 mmHg, and if a pulse was still detected at this level, the ABI was classified as “incompressible” [16]. The higher of the brachial artery pressures was used as the denominator [17]. Prevalent PAD was defined when at least one leg had a value $ABI < 0.90$, whereas “normal” was defined when both legs had values $0.90 \leq ABI \leq 1.40$.

Prospective analyses

Participants—To be included in the prospective analyses we required that participants have ABI measured at Exam 1, and have completed the Exam 2 (2002–2004) sleep questionnaire. Of the 6,233 participants who met these criteria, we excluded 868 participants with prevalent PAD ($ABI < 0.90$, $N=280$), or $ABI > 1.40$ ($N=42$) at baseline, those with no follow-up measurements ($N=324$), and those with incomplete data ($N=222$), resulting in a final analytic sample of 5,365 participants (Supplemental Figure 2).

Exposures—A sleep questionnaire was administered at exam 2 (2002–2004), and participants were categorized as having physician diagnosed sleep apnea, habitual snoring, or a normal sleep breathing pattern according to the following criteria. Physician diagnosed sleep apnea was defined if they answered “yes” to the following question: “Have you ever been told by a doctor that you had sleep apnea (a condition in which breathing stops briefly during sleep)?” Choices included yes, no and don’t know. Snoring frequency was defined by: “Have you ever snored (now or at any time in the past)?” Choices included: yes, no and don’t know. “How often do you snore now?” Choices include: do not snore anymore, sometimes (up to 2 nights a week), frequently (3–5 nights a week), always or almost always (6–7 nights a week) and don’t know. Individuals with habitual snoring were identified based on answering affirmatively to snoring greater than or equal to 3–5 days/week. Participants who did not have physician diagnosed apnea nor habitual snoring were classified as having a “normal sleep breathing pattern”. People who did not answer or answered “don’t know” for both the diagnosed sleep apnea and habitual snoring questions were excluded.

Incident PAD—Incident PAD was defined when at least one leg had a value of $ABI < 0.90$ at exam 3 and/or 5, whereas “normal” was defined when both legs continued to have values $0.90 \leq ABI \leq 1.40$. ABI was not measured at Exams 2 or 4. In sensitivity analyses, we also counted hospitalized PAD cases as incident PAD; in this analysis incident PAD was defined a) by a value of $ABI < 0.90$ at exam 3 and/or 5, or b) by having ICD codes indicative of treatment for PAD including bypass, angioplasty or stent placement in femoral, popliteal or iliac arteries by the end of follow-up.

Other variables, for both the cross-sectional and prospective analyses

MESA data collection protocols were similar (and typically identical) across clinic examinations. Sex, age, socioeconomic status (educational attainment: <high school, high school, some college or Bachelor's degree, or higher), cigarette smoking (pack-years, and current, former, never), physical activity, and use of cholesterol-lowering, anti-hypertensive, and diabetes medications were self-reported. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured at the level of the umbilicus. Resting blood pressure was measured three times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida). The average of the last two measurements was used. Fasting serum glucose was measured by rate reflectance spectrophotometry using thin film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY). Diabetes was defined as fasting glucose ≥ 126 mg/dl or use of insulin or hypoglycemic medication. Total cholesterol was measured (Roche Diagnostics, Indianapolis, IN 46250). HDL cholesterol was assessed in EDTA plasma using the cholesterol oxidase method (Roche Diagnostics) after precipitation of non-HDL-cholesterol with magnesium/dextran, and LDL cholesterol was calculated in plasma specimens having a triglyceride value < 400 mg/dl using the Friedewald formula. Serum assays were performed at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, MN). Variables for the cross-sectional analyses were from exam 5, and those for the longitudinal analyses were from exam 1.

Statistical analyses

Cross-Sectional analyses—Descriptive characteristics of participants were presented as means and proportions, stratified by categories of sleep apnea severity (AHI < 5 , 5–15, 15–30, ≥ 30), and sleep duration (< 6.0 , 6.0–6.9, 7.0–7.9, ≥ 8.0 h). Covariate-adjusted prevalence ratios (PRs) of PAD defined by ABI < 0.90 according to sleep categories were calculated using the generalized linear model. Standard errors of PRs were calculated using robust sandwich variance estimates[18].

We examined four sequential models: Model 1 included age, sex, race/ethnicity (black, non-black), and educational attainment; Model 2 additionally included physical activity (logarithmically transformed), tobacco use and pack-years; Model 3 further included BMI and waist circumference, and Model 4 additionally included major cardiovascular disease risk factors (diabetes, systolic blood pressure, hypertension medication use, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and cholesterol-lowering medication use).

Prospective analyses—Descriptive characteristics of participants were presented as means and proportions, stratified by categories: diagnosed sleep apnea, habitual snoring, normal sleep breathing pattern. Cox proportional hazards models were used to assess the relationship between sleep categories and incidence of PAD. When defining incident PAD by ABI < 0.90 , time of the event was the midpoint between exams.

In the Cox regression analyses, we examined four sequential models (Model 1 – Model 4) adjusting for exam 1 covariates, using the same modeling approach as in the cross-sectional analyses. The proportional hazards assumption was evaluated by testing the interaction between sleep categories and log(time), and by inspection of ln(-ln) survival curves for sleep categories.

Sensitivity analyses—For both the cross-sectional and prospective analyses, we evaluated whether age, sex, BMI, diabetes and race/ethnicity were effect modifiers of the relationship between sleep apnea or sleep duration and prevalent or incident PAD using Wald tests of cross-product terms in Model 1. Due to small cell sizes for some race/ethnicity and sleep apnea categories, we collapsed the race/ethnicity variable into black and non-black for the analysis. Additionally, interaction of marital status was tested in the prospective analysis to assess the potential influence of misclassification according to marital status. We also explored associations using an alternate cutpoint of ABI<1.00 to define incident PAD. Additionally for incident PAD, we evaluated the impact of adjusting for baseline ABI.

Results

Cross-sectional associations of objectively measured sleep and prevalent PAD

Among the analytic sample of 1,844 participants [average 63.0 years old, 54.1% female], a total of 101 (5.4%) were identified as having PAD (ABI<0.90). Nearly half of the prevalent PAD cases (n = 49) were in black participants.

Table 1 shows the characteristics of participants according to sleep apnea categories. In this sample, 14.7% were classified as having severe sleep apnea (AHI≥30), 18.4% as having moderate sleep apnea (15≤AHI<30), 31.6% as having mild sleep apnea (5≤AHI<15), and 35.2% as having a normal breathing pattern in sleep (AHI<5). Participants with severe sleep apnea were more likely to be male, hypertensive, diabetic, hyperlipidemic, and have high BMI and waist circumference (Table 1).

As shown in Table 2, sleep apnea severity was not significantly associated with prevalent PAD, regardless of the degree of adjustment. The fully adjusted prevalence ratio (PR) and 95% confidence interval (CI) for severe sleep apnea (AHI≥30) compared with normal (AHI<5) was 1.38 (0.77–2.45). There was no evidence that relations between sleep apnea and prevalent PAD were modified by age, sex, BMI, diabetes, or sleep duration ($p=0.57$, $p=0.57$, $p=0.12$, $p=0.65$, and $p=0.97$, respectively). There was, however, some evidence of qualitative interaction with race/ethnicity (black vs non-black) (p for interaction=0.05). In stratified analyses, a positive association was observed only among black participants; the PRs (95% CIs) for severe sleep apnea (AHI≥30) compared with normal (AHI<5) was 2.29 (1.07–4.89) in blacks, and 0.69 (0.29–1.64) in non-blacks (Model 4).

Supplemental Table 1 shows the characteristics of participants according to sleep duration categories. In this sample, 30.3% were classified as short sleepers (<6.0 hours/night of sleep per night), 31.7% as sleeping 6 to <7 hours, 27.0% as sleeping 7 to <8 hours (reference), and 11.0% as long sleepers (>8.0 hours/night). Compared to the reference group, participants who were short sleepers were more likely to be male, black, have a high BMI and waist

circumstance, and a worse overall CVD risk factor profile. As shown in Table 2, short sleep duration was positively associated with prevalent PAD. Relative to reference category, short sleepers had a higher prevalence of PAD after adjustment for demographics, lifestyle factors, adiposity [1.84 (1.03–3.28)], and other PAD risk factors [1.80 (0.98–3.31)]. Participants with long sleep duration also had higher prevalence of PAD in the fully-adjusted model; the PR and 95% CI compared with the reference category was 1.99 (1.01–3.92). There was no evidence that either age, sex, BMI, race/ethnicity, diabetes or sleep apnea severity modified relations between short or long sleep duration and prevalent PAD ($p=0.46$, $p=0.74$, $p=0.35$, $p=0.93$, $p=0.82$ and $p=0.97$, respectively).

Other sleep measurements, including the average oxyhemoglobin saturation during sleep, and percentage time during sleep with an oxygen saturation <90%, and the arousal index, were not associated with prevalent PAD (Supplemental Table 2).

Longitudinal association of self-reported sleep apnea with incident PAD

The 5,365 participants in our final analytic sample for prospective analyses were on average 61 years old at baseline, and 52% female. Over a median of 9.2 years (maximum = 11.2 years) of follow-up, a total of 229 incident PAD cases occurred, yielding a crude total PAD incidence rate of 5.5 per 1000 person-years.

Table 3 shows the characteristics of participants according to sleep apnea categories at baseline. In this sample of 5,365 participants with no PAD, 3.4% self-reported having been diagnosed with sleep apnea, 22.8% were habitual snorers, and 73.8% reported neither snoring nor sleep apnea. Participants with self-reported sleep apnea were more likely to be male, younger, black race, current or former smokers, have greater educational attainment, and a worse cardiovascular risk factor profile.

As shown in Table 4, those self-reporting diagnosed sleep apnea were at greater risk of incident PAD, relative to those with a normal sleep breathing pattern. The demographics and lifestyle factors-adjusted HR (95% CI) for participants reporting diagnosed sleep apnea compared to those without reported sleep apnea or habitual snoring was 1.88 (1.04–3.41). The associations were comparable in models with further adjustment for adiposity [1.74 (0.95–3.17)] and PAD risk factors [1.93 (1.05–3.53)]. Habitual snoring was not significantly associated with incident PAD. Results were similar when we also adjusted for marital status (data not shown). When we further adjusted for baseline ABI, the results between sleep apnea and incident PAD were similar. The HR (95% CI) for incident PAD among those with diagnosed apnea versus a normal sleep breathing pattern in the fully adjusted model was 2.14 (1.16–3.95). As a sensitivity analysis, we included hospitalized PAD cases which occurred by Exam 5 (N=25) as incident PAD. The association was comparable; the fully adjusted HR (95% CI) for incident PAD among those with diagnosed apnea was 1.77 (0.99–3.16).

There was no evidence that the relationships between diagnosed apnea and incident PAD were modified by age, sex, marital status, BMI, diabetes or race/ethnicity (black/non-black or 4 groups) ($p=0.85$, $p=0.93$, $p=0.29$, $p=0.81$, $p=0.62$, $p=0.89$, $p=0.16$, respectively).

Discussion

In this community-based racially/ethnically diverse sample we evaluated the cross-sectional association between objectively measured sleep characteristics and prevalent PAD, and the longitudinal association between self-reported sleep apnea and incidence of PAD over 9 years of follow-up. Longitudinally, self-reported sleep apnea was associated with greater incidence of PAD. In the cross-sectional analyses, there was suggestion of a race/ethnicity interaction, whereby objectively measured severe sleep apnea was associated with PAD prevalence in blacks, but not in other racial/ethnic groups. Also cross-sectionally, in the full study sample, those with short and long sleep duration were more likely to have prevalent PAD, compared to those getting 7 hours of sleep per night.

Prior studies evaluating the association between sleep apnea and PAD are sparse, but overall are consistent with our findings in blacks. Among 8,367 participants of the Hispanic Community Health Study/Study of Latinos who underwent an in-home sleep study, moderate-severe sleep apnea ($AHI \geq 15$) was independently associated with a 1.70 times higher prevalence of PAD[19]. Similarly, in a Taiwanese nationwide case-control study using population-based claims data, cases with sleep apnea diagnosed by clinical symptoms and/or $AHI \geq 5$ events/hr were 30% more likely to have been diagnosed with PAD than controls [20]. Additionally, in small clinical samples ($N \leq 100$), prevalent PAD among patients with suspected sleep apnea was high [21], as was prevalent sleep apnea among PAD patients needing surgical revascularization[22]. Sleep apnea defined by $AHI \geq 20$ was also associated with long-term morbidity and mortality after surgical revascularization in 84 PAD patients[23]. No prior studies have evaluated these associations among black individuals.

It is well established that blacks have a higher risk of PAD than Whites, even after accounting for traditional, clinical, biologic, and social risk factors[24]. In the present cross-sectional analyses, a positive association between sleep apnea and PAD was only observed among black participants. Data from the MESA also have shown that periodic limb movements during sleep, which can disturb sleep duration and continuity, are more likely to be associated with hypertension in black participants compared to white or Hispanic participants[25]. Although the results of analyses testing interactions in the MESA need to be interpreted cautiously due to the small number of events, these data raise the possibility that the effects of sleep disturbances on vascular disease may vary by race/ethnicity. Reasons for this that have been proposed include differences in sympathetic nervous system responses to sleep disturbances[25], as well as to differences in duration of lifetime exposure to sleep apnea[26].

In longitudinal analyses of self-reported physician diagnosed sleep apnea, there was no evidence for effect modification by race/ethnicity. Importantly, the recognition and diagnosis of sleep apnea in the community varies widely, and sleep apnea is often unrecognized using self-report, with the proportion of under-diagnosed cases varying by race/ethnicity [15]. Other factors that may explain the differences in our longitudinal and cross-sectional results include differences between incident and prevalent disease associations, as well as the possibility for chance findings.

The biological mechanisms that link sleep apnea to the development of PAD are likely similar to those through which sleep apnea influences coronary heart disease and stroke. Repetitive episodes of intermittent complete and partial airway collapse during sleep result in hypoxemia, hypercapnia, and repeated arousals from sleep. Acute hemodynamic changes[27] are associated with increased platelet aggregation[28] and fibrinogen concentrations[29], and decreased fibrinolysis[30]. Sleep apnea may accelerate atherosclerosis via sleep apnea-induced inflammation and oxidative stress, and subsequent endothelial dysfunction[31]. Individuals with sleep apnea have been shown to have more endothelial dysfunction, inflammation, and elevated oxidative stress than those without sleep apnea regardless of adiposity[32][33]. Additionally, sleep apnea has been associated with greater arterial stiffness[34][35]. Sleep apnea may also increase risk of PAD through hypertension, diabetes, and metabolic syndrome which are believed to result from sleep apnea-related sympathetic activation[36,37], oxidative stress[38], activation of the hypothalamic-pituitary-adrenal axis, and sleep loss or fragmentation. Furthermore, continuous positive airway pressure (CPAP) therapy has been shown to improve blood pressure and intermediate markers of vascular disease[39–41].

In our sample, both short- and long-sleepers had a higher prevalence of PAD. To our knowledge, no other study has evaluated the association between objectively assessed sleep duration and PAD. Possible mechanisms posited for the association between short sleep duration and PAD include change in circulating levels of leptin and ghrelin[42,43], which may increase the risk of obesity[42,44] via increased appetite and caloric intake and reduced energy expenditure[44,45], leading to hypertension[46], impaired glycemic control[47] and endothelial dysfunction[48]. Leptin may also activate the sympathetic system leading to increased blood pressure[49], and short sleep has also been linked to inflammation[3,50]. On the other hand, mechanisms for the association between long sleep duration and atherosclerosis are less clear. Long sleep duration has been associated with numerous factors which have been linked to atherosclerotic risk, such as low socioeconomic status, unemployment, depressive symptoms, and poor general health [51]. Of course, given the cross-sectional association we cannot exclude the possibility of reverse causality. As we did not have information for PAD symptoms, it is possible that some participants with critical ischemia may have had shortened sleep duration due to severe PAD symptoms.

Strengths of our study included the large multi-racial/ethnic population-based samples, comprehensive assessment of traditional cardiovascular risk factors using standardized data collection protocols, and objective measurement of PAD. An additional strength of the cross-sectional analyses was the use of objectively and rigorously measured indices of sleep apnea and sleep duration by in-home PSG and actigraphy. Our study also had limitations. First, ABI was only available at Exams 1, 3, 5; thus the date of PAD onset was unknown. Second, although the sample was quite large for a study using objective sleep measurements, given the limited number of prevalent and incident PAD cases we were underpowered for some analyses, particularly those stratified by racial/ethnic groups. However, analysis of black vs non-black may be a reasonable approach because the PAD prevalence in blacks was more than 2-times higher than in the other racial/ethnic groups[10]. Third, in the cross-sectional analyses, survival bias may have influenced results. Fourth, for the prospective analyses sleep apnea and habitual snoring were self-reported, thus misclassification almost certainly

occurred. Polysomnography is the gold-standard method for the assessment of OSA[52]. Studies based on self-report have limitations in accuracy, and OSA is known to be underdiagnosed in the community [52]. Likelihood of receiving an OSA diagnosis may also have been dependent on access to health care; in our sample those self-reporting OSA tended to have greater educational attainment. It is also possible that those with a clinical diagnosis of sleep apnea are more symptomatic and have more severe disease than those in whom sleep apnea is identified through an epidemiological study. Importantly, knowledge of snoring status and frequency may vary according to marital status, however our sensitivity analyses do not suggest that marital status had a major influence on our snoring findings. Ideally, we would have objective measures. Lastly, we cannot exclude the possibility of residual confounding resulting from unmeasured or inadequately controlled confounders.

In conclusion, in this racially/ethnically diverse community-based sample, we found evidence that objectively measured sleep apnea was associated with a higher prevalence of PAD in blacks. Additionally, both short and long sleep duration was associated with a higher prevalence of PAD in the overall sample. In prospective analyses, self-reported sleep apnea was associated with higher risk of incident PAD. These findings suggest that both sleep apnea and sleep quantity may influence peripheral atherosclerosis development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Sleep apnea is a potential, modifiable risk factor for peripheral artery disease.
- Self-reported sleep apnea was associated with greater risk of developing PAD.
- Objectively measured long/short sleep duration was associated with prevalent PAD.

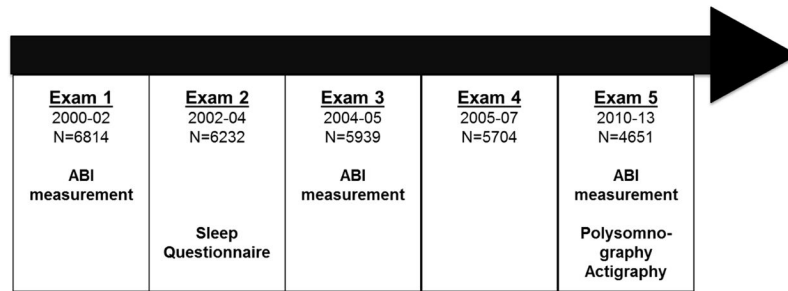


Fig. 1.
Overview of the Multi-Ethnic Study of Atherosclerosis timeline and measurements
ABI, ankle-brachial index.

Table 1

Participant characteristics according to apnea-hypopnea index categories: The Multi-Ethnic Study of Atherosclerosis 2010–2013

Sleep disordered breathing category	Normal	Mild	Moderate	Severe
AHI ^c	<5.0 n=650	5.0–14.9 n=583	15.0–29.9 n=340	≥30.0 n=271
Demographics				
Age, years ^a	66.9±8.9	69.1±9.2	68.8±8.9	68.8±9.1
Male, n (%)	209 (32.2%)	253 (43.4%)	195 (57.4%)	186 (68.6%)
Race/ethnicity, n (%)				
White	247 (38.0%)	221 (37.9%)	120 (35.3%)	84 (31.0%)
Chinese-American	79 (12.2%)	59 (10.1%)	43 (12.6%)	37 (13.7%)
Black	194 (29.8%)	161 (27.6%)	90 (26.5%)	75 (27.7%)
Hispanic	130 (20.0%)	142 (24.4%)	87 (25.6%)	75 (27.7%)
Education, n (%)				
< High School	94 (14.5%)	79 (13.6%)	51 (15.0%)	48 (17.7%)
High School Graduate	283 (43.5%)	278 (47.7%)	160 (47.1%)	122 (45.0%)
College	122 (18.8%)	114 (19.6%)	60 (17.6%)	53 (19.6%)
Graduate School	151 (23.2%)	112 (19.2%)	69 (20.3%)	48 (17.7%)
Lifestyle factors				
Physical activity, met-min/wk ^b	1980 (765, 4087)	1732 (690, 3510)	1890.0 (735, 3780)	1732 (690, 3150)
Cigarette smoking status, n (%)				
Never	323 (50.1%)	269 (46.3%)	160 (47.5%)	111 (41.0%)
Former	268 (41.6%)	270 (46.5%)	161 (47.8%)	139 (51.3%)
Current	54 (8.4%)	42 (7.2%)	16 (4.7%)	21 (7.7%)
Pack years, among ever/current smokers ^b	11 (2, 27)	13 (3, 29)	12 (3, 28)	9 (1, 29)
Current alcohol drinker, n (%)	276 (42.7%)	252 (43.4%)	146 (43.3%)	134 (49.4%)
Physiologic characteristics				
BMI, kg/m ² ^a	26.7±5.0	28.8±5.0	29.6±5.3	31.3±6.0
Waist circumference, cm ^a	93.9±13.6	99.7±13.0	102.2±12.7	105.9±14.4
Systolic blood pressure, mmHg ^a	120.7±21.3	123.4±19.4	123.2±18.7	125.6±19.5

Sleep disordered breathing category		Normal	Mild	Moderate	Severe
AHI ^c		<5.0 n=650	5.0–14.9 n=583	15.0–29.9 n=340	≥30.0 n=271
Diastolic blood pressure, mmHg ^a		67.3±9.9	68.2±9.7	69.6±9.7	70.3±9.7
Prevalent hypertension, n (%) ^d		328 (50.5%)	334 (57.3%)	199 (58.5%)	168 (62.0%)
Hypertension medication, n (%)		302 (46.5%)	318 (54.5%)	184 (54.1%)	160 (59.0%)
Cholesterol-lowering medication, n (%)		205 (31.5%)	224 (38.4%)	142 (41.8%)	110 (40.6%)
HDL cholesterol, mg/dl ^b		57 (47.70)	53 (45.64)	51 (42.59)	48 (41.58)
LDL cholesterol, mg/dl ^b		107 (85,130)	106 (85,127)	103 (81,129)	102 (82,124)
Triglycerides, mg/dl ^b		89 (66,118)	97 (71,137)	100 (73.0,134.0)	105 (79,144)
Prevalent diabetes, n (%) ^e		91 (14.1%)	98 (17.0%)	76 (22.6%)	70 (25.9%)
Sleep characteristics^a					
AHI ^c		2.1±1.5	9.3±2.9	20.7±4.1	48.0±15.1
Self-reported average sleep time per night, hours		6.7±1.2	6.5±1.4	6.4±1.4	6.3±1.5
Hypoxemia					
Average oxyhemoglobin Saturation, %		95.2±1.3	94.3±1.5	93.7±1.5	93.0±2.3
% Time with oxyhemoglobin Saturation<90%, %		0.7±3.7	2.7±7.9	5.2±8.6	11.8±14.3
Arousal index		16.9±8.3	20.1±9.2	25.0±10.8	36.5±14.0

^aRepresented as mean ± SD.^bRepresented as median (IQR).^cApnea hypopnea index, number of events per hour of sleep.^dHypertension diagnosed by JNC VI (1997) Criteria.^eDiabetes diagnosed by 2003 ADA Fasting Criteria.

All variables were obtained at exam 5.

Association of sleep apnea-hypopnea index and sleep duration with prevalent peripheral artery disease: The Multi-Ethnic Study of Atherosclerosis 2010–2013

Table 2

Sleep apnea						
Category	Normal	Mild	Moderate	Severe		
AHI	<5.0	5.0–14.9	15.0–29.9	≥30.0		<i>p</i> for trend
Total sample						
Median AHI	2.0	9.1	20.1	43.8		
N participants	650	583	340	271		
N PAD cases	31	31	20	18		
Prevalence ratio (95% CI) ^a						
Model 1	1.0 (ref)	0.99 (0.61–1.59)	1.19 (0.70–2.05)	1.53 (0.87–2.69)		0.15
Model 2	1.0 (ref)	1.03 (0.64–1.67)	1.22 (0.70–2.14)	1.53 (0.88–2.68)		0.14
Model 3	1.0 (ref)	0.96 (0.59–1.55)	1.17 (0.67–2.04)	1.51 (0.86–2.65)		0.15
Model 4	1.0 (ref)	0.90 (0.54–1.48)	1.11 (0.64–1.91)	1.38 (0.77–2.45)		0.26
Black participants						
Median AHI	1.9	9.4	20.3	46.4		
N participants	194	161	90	75		
N PAD cases	11	13	13	11		
Prevalence ratio (95% CI) ^a						
Model 1	1.0 (ref)	1.22 (0.58–2.55)	1.88 (0.88–4.04)	2.48 (1.15–5.36)		0.01
Model 2	1.0 (ref)	1.35 (0.63–2.89)	2.00 (0.90–4.46)	2.55 (1.16–5.64)		0.01
Model 3	1.0 (ref)	1.25 (0.60–2.57)	2.13 (0.99–4.58)	2.40 (1.13–5.10)		0.01
Model 4	1.0 (ref)	1.10 (0.54–2.25)	1.90 (0.92–3.94)	2.29 (1.07–4.89)		0.01
Non-black participants						
Median AHI	2.1	9.0	20.0	43.4		
N participants	456	422	250	196		
N PAD cases	20	18	7	7		
Prevalence ratio (95% CI) ^a						
Model 1	1.00	0.90 (0.48–1.70)	0.76 (0.32–1.80)	0.99 (0.41–2.38)		0.78
Model 2	1.00	0.87 (0.47–1.62)	0.73 (0.30–1.80)	1.05 (0.46–2.39)		0.83

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Model 3	1.00	0.73 (0.39–1.38)	0.54 (0.21–1.36)	0.78 (0.33–1.85)	0.35
Model 4	1.00	0.70 (0.37–1.32)	0.51 (0.20–1.28)	0.69 (0.29–1.64)	0.24
Sleep duration					
Category	Short	Moderately short	Reference	Long	<i>p</i> -value ^b
Sleep duration	<6 hours	6–7 hours	7–8 hours	>8 hours	
Median sleep duration	5.2	6.5	7.4	8.4	
N participants	559	585	498	202	
N PAD cases	38	27	18	17	
Prevalence ratio (95% CI) ^a					
Model 1	1.73 (1.00–3.00)	1.32 (0.74–2.36)	1.0 (ref)	1.82 (0.96–3.44)	0.17
Model 2	1.79 (1.02–3.15)	1.40 (0.79–2.49)	1.0 (ref)	1.86 (0.96–3.59)	0.16
Model 3	1.84 (1.03–3.28)	1.46 (0.82–2.61)	1.0 (ref)	1.87 (0.96–3.67)	0.16
Model 4	1.80 (0.98–3.31)	1.61 (0.88–2.94)	1.0 (ref)	1.99 (1.01–3.92)	0.18

Model 1: Adjusted for age, sex, race/ethnicity and educational attainment.

Model 2: Adjusted for Model 1 + log(physical activity) + smoking status + pack years.

Model 3: Adjusted for Model 2 + Adiposity (body mass index, waist circumference).

Model 4: Adjusted for Model 3 + PAD risk factors (presence of diabetes, systolic BP, hypertension medication use, HDL-C, LDL-C, use of cholesterol-lowering medications).

^aPrevalence ratio calculated from general linear model of Poisson family with robust variance.

^b*p*-value from 3-df Wald test.

AHI, Apnea-Hypopnea Index; CI, Confidence Interval; PAD, Peripheral Artery Disease.

All variables were obtained at exam 5.

Bolded variables are associated with prevalent PAD (*p* < 0.05).

Table 3

Participant characteristics according to self-reported sleep apnea categories: The Multi-Ethnic Study of Atherosclerosis 2000–2002

Sleep apnea category	Normal sleep breathing pattern n=3959	Habitual snoring n=1224	Sleep apnea n=182
Demographics			
Age, years ^a	61.9±10.1	59.0±9.1	59.6±9.1
Male, n (%)	1,710 (43.2%)	722 (59.0%)	123 (67.6%)
Race/ethnicity, n (%)			
White	1,657 (41.9%)	420 (34.3%)	86 (47.3%)
Chinese-American	473 (11.9%)	183 (15.0%)	8 (4.4%)
Black	1,039 (26.2%)	269 (22.0%)	55 (30.2%)
Hispanic	790 (20.0%)	352 (28.8%)	33 (18.1%)
Education, n (%)			
< High School	604 (15.3%)	230 (18.8%)	10 (5.5%)
High School Graduate	693 (17.5%)	218 (17.8%)	25 (13.7%)
College	1,893 (47.8%)	547 (44.7%)	102 (56.0%)
Graduate School	769 (19.4%)	229 (18.7%)	45 (24.7%)
Lifestyle Factors			
Physical activity, met-min/wk ^b	1,680 (750, 3,270)	1,331 (540, 2,918)	2,220 (885, 4,121)
Cigarette smoking status, n (%)			
Never	2,097 (53.0%)	579 (47.3%)	73 (40.1%)
Former	1,415 (35.7%)	473 (38.6%)	79 (43.4%)
Current	447 (11.3%)	172 (14.1%)	30 (16.5%)
Pack years, among ever/current smokers ^b	14 (5, 30)	16 (5, 30)	19 (8, 38)
Current alcohol drinker, n (%)	2,257 (57.0%)	721 (58.9%)	120 (65.9%)
Physiologic characteristics			
BMI, kg/m ² ^a	27.6±5.1	29.6±5.6	32.1±6.2
Waist circumference, cm ^a	96.1±13.8	101.4±14.1	108.4±15.1
Systolic blood pressure, mmHg ^a	124.9±20.7	125.0±19.8	125.3±19.2
Diastolic blood pressure, mmHg ^a	71.2±10.0	73.6±10.2	73.7±9.9

Sleep apnea category	Normal sleep breathing pattern n=3959	Habitual snoring n=1224	Sleep apnea n=182
Prevalent hypertension, n (%) ^c	1,652 (41.7%)	504 (41.2%)	94 (51.6%)
Hypertension medication, n (%)	1,348 (34.1%)	424 (34.7%)	89 (48.9%)
Cholesterol-lowering medication, n (%)	613 (15.5%)	182 (14.9%)	51 (28.0%)
HDL cholesterol, mg/dl ^b	50 (41, 61)	46 (39, 55)	45 (38, 56)
LDL cholesterol, mg/dl ^b	115 (96, 136)	118 (98, 138)	112 (90, 131)
Triglycerides, mg/dl ^b	108 (76, 155)	122 (84, 176)	112 (85, 167)
Prevalent diabetes, n (%) ^d	398 (10.1%)	148 (12.2%)	22 (12.1%)

^aRepresented as mean ± SD.

^bRepresented as median (IQR).

^cHypertension diagnosed by JNC VI (1997) Criteria.

^dDiabetes diagnosed by 2003 ADA Fasting Criteria.

All variables were obtained at exam 1, except for sleep apnea categories.

Association of sleep disordered breathing with risk of incident peripheral artery disease: The Multi-Ethnic Study of Atherosclerosis 2000–2010

Table 4

Sleep apnea category	Normal	Habitual snoring	Diagnosed apnea
Participants (n)	3959	1224	182
Person-years	30283	9596	1445
Incident PAD (n)	170	47	12
Hazard ratios (95% Confidence Intervals)			
Model 1	1.00	1.23 (0.89–1.71)	2.12 (1.17–3.84)
Model 2	1.00	1.25 (0.90–1.74)	1.88 (1.04–3.41)
Model 3	1.00	1.19 (0.85–1.66)	1.74 (0.95–3.17)
Model 4	1.00	1.19 (0.84–1.67)	1.93 (1.05–3.53)

Model 1: Adjusted for age, sex, race/ethnicity, and educational attainment.

Model 2: Adjusted for Model 1 + log(physical activity) + smoking status + pack years.

Model 3: Adjusted for Model 2 + Adiposity (body mass index, waist circumference).

Model 4: Adjusted for Model 3 + PAD risk factors (presence of diabetes, systolic BP, hypertension medication use, HDL-C, LDL-C, use of cholesterol-lowering medications).

All variables were obtained at exam 1, except for sleep apnea categories.

Bolded variables are associated with incident PAD ($p < 0.05$).