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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 1844 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 evaluated the relation between self-reported diagnosed sleep apnea and PAD incidence in 5365 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 7 h/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.

1. 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

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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 [9,10].

Peripheral artery disease (PAD) affects approximately 8.5 million Americans (7.2% of the population) aged 40 years or older [11] 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 [12], 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 [13] and subclinical atherosclerotic markers [e.g. intimal medial thickness and coronary artery calcium] [14], 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.

2. Materials and methods

2.1. Participants

The MESA [15] cohort includes 6814 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 Fig. 1. Local institutional review boards approved study protocols, and all participants gave written informed consent.

2.2. Cross-sectional analyses

2.2.1. Participants

All 4077 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 [16]. Of the remaining 3789 participants, 2261 participated in the sleep exam (59.7%). As has been reported elsewhere [16], 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 1922 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 1844 participants (Supplemental Fig. 1).

2.2.2. Exposures

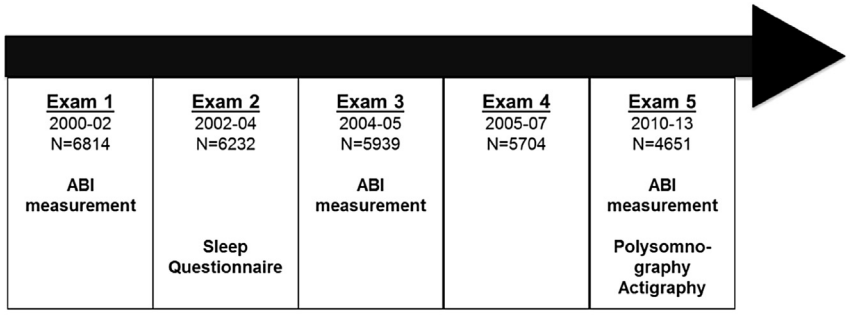
An overnight unattended in-home polysomnogram was conducted following a standardized protocol using a 15-channel monitor, Compumedics Somte System (Compumedics LTd., Abbottsville, Australia), as described elsewhere [16].

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 ≥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-s epochs as sleep or wake using Actiware-Sleep version 5.59 software as previously described [16]. Participants were categorized into four sleep duration groups: <6.0, 6.0–6.9, 7.0–7.9 (reference), and ≥8.0 h.

2.2.3. 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" [17]. The higher of the brachial artery pressures



ABI, ankle-brachial index.

Fig. 1. Overview of the Multi-Ethnic Study of Atherosclerosis timeline and measurements.