Sleep Apnea Is Independently Associated With Peripheral Arterial Disease in the Hispanic Community Health Study/Study of Latinos


Objective—Sleep apnea (SA) has been linked with various forms of cardiovascular disease, but little is known about its association with peripheral artery disease (PAD) measured using the ankle–brachial index. This relationship was evaluated in the Hispanic Community Health Study/Study of Latinos.

Approach and Results—We studied 8367 Hispanic Community Health Study/Study of Latinos participants who were 45 to 74 years of age. Sleep symptoms were examined with the self-reported Sleep Health Questionnaire. SA was assessed using an in-home sleep study. Systolic blood pressure was measured in all extremities to compute the ankle–brachial index. PAD was defined as ankle–brachial index <0.90 in either leg. Multivariable logistic regression was used to investigate the association between moderate-to-severe SA, defined as apnea–hypopnea index ≥15, and the presence of PAD. Analyses were adjusted for covariates. The prevalence of PAD was 4.7% (n=390). The mean apnea–hypopnea index was significantly higher among adults with PAD compared with those without (11.1 versus 8.6 events/h; P=0.046). After adjusting for covariates, moderate-to-severe SA was associated with a 70% increase in the odds of PAD (odds ratio, 1.7; 95% confidence interval, 1.1–2.5; P=0.0152). This association was not modified by sex (P=0.8739). However, there was evidence that the association between moderate-to-severe SA and PAD varied by Hispanic/Latino background (P<0.01). Specifically, the odds were stronger in Mexican (adjusted odds ratio, 2.9; 95% confidence interval, 1.3–6.2) and in Puerto Rican Americans (adjusted odds ratio, 2.0; 95% confidence interval, 0.97–4.2) than in other backgrounds.

Conclusions—Moderate-to-severe SA is associated with higher odds of PAD in Hispanic/Latino adults. (Arterioscler Thromb Vasc Biol. 2015;35:710-715. DOI: 10.1161/ATVBHA.114.304625.)

Key Words: ankle–brachial index ■ atherosclerosis ■ Hispanic Americans ■ peripheral arterial disease ■ sleep apnea syndromes

We recently reported the prevalence of mild, moderate, and severe sleep apnea (SA) in the US Hispanic/Latino population to be 25.8%, 9.8%, and 3.9%, respectively.1 SA occurs when the upper airway collapses during sleep resulting in a cycle of hypoxemia, increased respiratory effort, frequent arousals, and increased sympathetic activity. The apnea–hypopnea index (AHI) is calculated as the sum of apneas and hypopneas per hour of sleep. Clinically significant SA is considered to be of at least moderate severity, defined as AHI ≥15 per hour.

SA is associated with cardiovascular morbidity and mortality and is an independent risk factor for coronary artery disease and stroke.2,4 Atherosclerosis has been proposed as an intermediate between SA and incident cardiovascular disease events.3 Numerous studies5-22 have explored the relationship between SA and measures of atherosclerotic vascular disease in clinical or population-based samples. Such studies have examined the end point of carotid artery intima-media thickness and reported a significant positive association between SA and increased carotid artery intima-media thickness.5,10-13,15-17,21,23-24 Importantly, to our knowledge, no study to date has investigated the association between SA and the ankle–brachial index (ABI), an indicator of significant obstructive peripheral atherosclerotic burden in the lower extremities that independently predicts mortality.25

To address the limitations of the current literature, we evaluated the association between SA and peripheral artery disease (PAD) among participants enrolled in the Hispanic Community Health Study/Study of Latinos. We also assessed...
the role of sex and Hispanic/Latino groups defined by place of birth or family background as potential effect modifiers of this association.

Material and Methods
Material and methods are available in the online-only Data Supplement.

Results
Among a total of 16,415 Hispanic Community Health Study/Study of Latinos participants, those younger than 45 years of age were not assessed for ABI, resulting in exclusion of 6710 participants. Of the remaining participants, 1110 (6.76%) had missing ABI data, and 189 (1.15%) had an ABI >1.4 in either or both legs. Therefore, the analytic sample for this study consisted of 8367 individuals.

The overall prevalence of PAD was 4.7% (n=390). Compared with those without PAD, participants with PAD were older (mean age, 61 versus 56 years; P<0.0001) and more often women (67% versus 55%; P=0.0001). The mean body mass index was not significantly different between the 2 groups. As expected, the prevalence of comorbidities, such as hypertension, coronary heart disease (CHD), and diabetes mellitus were higher in the PAD group compared with the non-PAD group. Similarly, ≥10 pack-years of smoking history was more common in the group with PAD (39% versus 24%).

The mean AHI was significantly higher among adults with PAD compared with those without PAD (11.1 versus 8.6 events/h; P=0.046; Table 1). However, there was no statistically significant difference in self-reported sleep duration, mean baseline oxygen saturation, and mean sleep time spent with oxygen <90% between the 2 groups (data not shown).

Table 2 shows the odds ratios (OR) from the multivariable model assessing the relationship between no to mild SA (AHI<15) to PAD. After adjusting for age, sex, body mass index, waist:hip ratio, hypertension, CHD, diabetes mellitus, dyslipidemia, C-reactive protein levels, smoking, alcohol use, physical activity, study site, and Hispanic/Latino background, individuals with moderate-to-severe SA were 1.67 (95% confidence interval [CI], 1.10–2.51) times more likely to have PAD. This association was not modified by sex (P=0.8739). However, there was evidence that the association between moderate-to-severe SA and PAD was different by Hispanic/Latino background (P=0.0001). Specifically, the odds were stronger in Mexican (adjusted OR, 2.9; 95% CI, 1.3–6.2) and in Puerto Rican Americans (adjusted OR, 2.02; 95% CI, 0.97–4.2) than in other backgrounds listed in Table 1. The statistical power was inadequate to test this in other Hispanic/Latino groups.

Further analyses also assessed the relationship between increasing severity of SA and PAD (Table 3). Here, the reference group consisted of individuals with an AHI<5. Three other categories reflecting increasing AHI severity were defined as 5 to <15 events/h, 15 to <30 events/h and ≥30 events/h. In an adjusted model, AHI 15 to <30 (moderate SA) was associated with a 90% increase in the odds of PAD as compared with AHI<5 (OR, 1.90; 95% CI, 1.15–3.14). The OR for AHI≥30, which defines severe SA, was not statistically significant but had a wide CI (versus AHI<5; OR, 1.21; 95% CI, 0.62–2.38).

We conducted a sensitivity analysis that excluded participants with prevalent CHD, and we found similar results (data not shown). We also assessed the independent relationship of PAD with sleep variables other than AHI. In a multivariate logistic regression model, there was no significant association between T90 and lowest oxygen saturation with PAD after adjustment for age, sex, study site, Hispanic background, income, physical activity, and C-reactive protein levels (data not shown).

Discussion
To our knowledge, this is the first study to assess the independent association between SA and PAD in a large community-based cohort. We studied a diverse sample of Hispanics/Latinos, representing the largest minority population, residing within the United States. We found that the presence of moderate-to-severe SA was associated with a 67% increase in the odds of PAD, as measured by the ABI. These findings are independent of age, sex, body mass index, waist:hip ratio, hypertension, CHD, diabetes mellitus, dyslipidemia, C-reactive protein levels, smoking, alcohol use, physical activity, study site, and Hispanic/Latino background. The magnitude of this association was not modified by sex. Furthermore, the odds were stronger in Mexican and Puerto Rican Americans than in other backgrounds, reflecting either the play of chance or differences in prevalence and severity of these conditions across national backgrounds. No increase in risk of PAD was observed until an AHI of 15 was reached.

SA has been associated with numerous cardiovascular conditions, including hypertension,26 CHD,47 cardiac arrhythmias, heart failure,29,30 stroke,31 and sudden death.32 Plausible mechanisms that may contribute to an overall increased vascular risk in the setting of SA include dyslipidemia,33 glucose intolerance,34 diabetes mellitus,35 sympathetic activation,36 systemic inflammation,37,38 endothelial dysfunction,19,39 oxidative stress,40 and autonomic dysfunction.41 Our study contributes to the literature linking SA with subclinical markers of vascular disease risk, which include several previous studies of the coronary and cerebrovascular beds.6,12,13,21,42 SA is associated with increased carotid artery atherosclerosis and treatment of SA seems to decrease and reverse carotid artery atherosclerosis.43,44 Evidence also suggests that increasing severity of SA is independently associated with increased carotid artery plaque burden.12,17,23,42,45 Similarly, current evidence suggests an independent link between SA and coronary artery atherosclerosis measured both invasively and noninvasively.46-48

<table>
<thead>
<tr>
<th>Nonstandard Abbreviations and Acronyms</th>
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<td>ABI</td>
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<td>AHI</td>
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<td>CI</td>
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However, until this study similar evidence for the association between SA and PAD was lacking. PAD affects $\approx 20\%$ of individuals $>60$ years and can cause disabling symptoms because of claudication.$^{49}$ PAD is a marker of underlying atherosclerosis severity and prognosis, which shares many risk factors with SA, including hypertension, obesity, and diabetes mellitus.$^{50-52}$ A small study of patients with severe PAD who were awaiting surgical intervention reported a prevalence of undiagnosed SA of $85\%$ (n=70/82).$^{53}$ This study had several limitations, including small sample size, lack of population-based study sample, and representation of the entire spectrum of PAD severity. In our study, PAD was assessed with the use of ABI, a noninvasive, reliable, inexpensive, and readily available technique that is typically used to diagnose subclinical and clinical PAD. More specifically, we used an abnormal ABI ($<0.90$) in either leg to indicate peripheral atherosclerosis, which compared with other non-invasive measures of atherosclerosis, typically requires more extensive burden of disease.

The Hispanic Community Health Study/Study of Latinos assessed SA with an in-home sleep study as opposed to in-laboratory full night attended polysomnography. This approach may modestly underestimate SA severity and does not allow assessment of sleep stages, duration, and fragmentation. Variation in recording times across individuals may have contributed to some misclassification of the AHI in cases when rapid eye movement sleep was not adequately represented. However, we found no association between recording time and either AHI or ABI (data not shown). Furthermore, our data are cross-sectional and, therefore, cannot establish a cause–effect relationship between SA and PAD. Adjustment for a full range of potential confounders nonetheless does not exclude the possibility of residual confounding.

We conducted a sensitivity analysis where we excluded prevalent CHD participants and we found similar results (data not shown). SA may, therefore, be associated with PAD independent of prevalent CHD. Our study was not designed to address the relative atherosclerotic effect of SA on different vascular beds, that is, coronary versus peripheral. Future work is recommended to understand whether SA is worse for the peripheral arteries than coronary or carotid arteries.

In analyses of the dose–response relationship between SA severity and the odds of PAD (Table 3), we did not
Table 3. Relationship Between Severity of SA and PAD

<table>
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<tr>
<th>Severity of SA</th>
<th>% PAD (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
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<tr>
<td>AHI 5 to 15 (n=4432)</td>
<td>4.47 (3.57–5.60)</td>
<td>Reference level</td>
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<tr>
<td>AHI 5–15 (n=1859)</td>
<td>4.37 (3.29–5.77)</td>
<td>0.97 (0.65–1.46)</td>
</tr>
<tr>
<td>AHI 15 to 30 (n=686)</td>
<td>7.88 (5.39–11.38)</td>
<td>1.90 (1.15–3.14)</td>
</tr>
<tr>
<td>AHI≥30 (n=381)</td>
<td>5.32 (2.99–9.29)</td>
<td>1.21 (0.62–2.38)</td>
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</tbody>
</table>

Odds ratio is adjusted for age, sex, study site, Hispanic/Latino background, education, income, body mass index, pack-years smoking, hypertension, coronary heart disease, diabetes mellitus, dyslipidemia, waist/hip ratio, physical activity, and highly sensitive C-reactive protein. AHI indicates apnea–hypopnea index; CI, confidence interval; PAD, peripheral arterial disease; and SA, sleep apnea.

find consistently increasing risk with increasing SA severity. Secondary analyses modeling AHI as categorical levels showed that the strongest association between SA and PAD was in the moderate SA group (OR, 1.90; 95% CI, 1.15–3.14). The lack of significant association in the severe SA group may have been because of the sample size limitations, which may be clarified in future studies about dose–response relationship.

Finally, we noted that Hispanic/Latino group seems to modify the relationship between SA and PAD, with stronger effects for Mexicans and Puerto Ricans relative to other backgrounds (Table 1). In our sample, Puerto Ricans had the highest prevalence of obesity (50.2%; SE, 2.32) when compared with the other Hispanic/Latino backgrounds, which may partly explain the stronger effects, noted in that group. The statistical power to explore the pattern of effect modification, however, was insufficient for the other backgrounds. We found no evidence that sex modified the relationship between SA and PAD.

This study included a population-based, rather than a referral or clinic-based sample, and thus is less influenced by selection biases than other cited research.44 Our Hispanic/Latinos US study population has long been recognized to have high obesity risk and is now documented to have high prevalence of SA.45 Previous studies evaluating the association between SA and subclinical peripheral atherosclerosis have not used the ABI, which is routinely available in a clinical setting and, therefore, is relatively accessible and at low cost.

Finally, the methods of measurement of SA and PAD were objective and standardized as part of this large multicenter National Institutes of Health-sponsored cohort study.

Acknowledgments

We thank the staff and participants of Hispanic Community Health Study/Study of Latinos for their important contributions.

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Disclosures

Y. Teng and D. Sotres-Alvarez had full access to the study data and take responsibility for the integrity of the data and accuracy of analyses. All authors have reviewed and approved the final manuscript. None of the authors had any financial or other conflicts of interest.

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**Significance**

To our knowledge, this is the first study to assess the independent association between sleep apnea and peripheral artery disease in a large community-based cohort. We studied a diverse sample of Hispanics/Latinos, representing the largest American minority population, residing within the United States. We found that the presence of moderate-to-severe sleep apnea was associated with a 67% increase in the odds of peripheral artery disease, as measured by the ankle–brachial index. These findings are independent of age, sex, body mass index, waist:hip ratio, hypertension, coronary heart disease, diabetes mellitus, dyslipidemia, C-reactive protein levels, smoking, alcohol use, physical activity, study site, and Hispanic background is evident in both men and women. Furthermore, we found that the strength of this association was modified by Hispanic/Latino group. Specifically, the odds were stronger in Mexican and Puerto Rican Americans than in other backgrounds. Future studies are needed to address whether peripheral artery disease improves with sleep apnea treatment. Further research may assess whether sleep apnea variably influences the atherosclerotic process in different vascular beds.
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Material and Methods

Study Population
The HCHS/SOL is a community based cohort study consisting of 16,415 self-identified Hispanic/Latino participants aged 18 to 74 years residing in four U. S. urban areas (Bronx, NY; Chicago, IL; Miami, FL; San Diego, CA). The details of the study design, sampling strategy, and recruitment are described elsewhere. In brief, all participants underwent a baseline interview and an extensive clinic examination (2008-2011) that included, but was not limited to, anthropometry, electrocardiogram (ECG), blood pressures in both arms, phlebotomy, glucose tolerance testing, audiology, lung function tests and oral examinations. Questionnaires included sociodemographics, health and medical history, smoking, alcohol, occupational history and physical activity. Medication use was ascertained by MDDB (Medi-Span Master Drug Data base) Product line Therapeutic Classification System and also by directed questions about specific types of medications.

Individuals younger than 45 years of age (n=6,710) were excluded from this study, as they did not undergo ankle brachial index measurement. Individuals with ABI values >1.4 in either leg (n=189) were excluded as these individuals are considered to have stiff arteries likely due to medial artery sclerosis which may result in an artificially elevated ABI value. Sleep studies with fewer than 30 minutes defined as incomplete (n=1,110) were excluded from all analyses. These non-exclusive criteria resulted in an analytic sample size of 8,367 participants.

Assessment of Ankle Brachial Index
Ankle brachial index measurements were obtained for all HCHS/SOL participants aged 45-74 years. Briefly, after resting quietly for 5 minutes, a Doppler probe was used to obtain systolic blood pressures (SBP) in the following order: right brachial artery, right dorsalis pedis artery, right posterior tibial artery, left posterior tibial artery, left dorsalis pedis artery and left brachial artery. Two separate ABIs were generated, one for each leg. The denominator for both ABIs was the highest SBP from either the left or right brachial artery. For each leg, the numerator was the higher of the two lower extremity measurements, i.e. posterior tibial SBP or dorsalis pedis SBP. PAD was defined as ABI < 0.9 in either leg.

Assessment of Sleep Symptoms and Sleep Apnea
Both subjective (questionnaire) and objective (overnight home study) sleep data were collected. The sleep questionnaire (interview-administered by study staff) included the Sleep Heart Health Study Sleep Habits questionnaire to assess symptoms of SA and sleep patterns, and the Epworth Sleepiness Scale to assess daytime sleepiness. Objective sleep apnea testing included measurement of overnight oxygen saturation (using a transcutaneous oximeter), airflow (using nasal cannula and pressure transducer), snoring sounds (by microphone) and head position and movement (ARES Unicorder 5.2; B-Alert, Carlsbad, CA). Each participant underwent a self-administered test at home after receiving, during the baseline clinic visit, in-person demonstration and instruction on the application of the monitor. Sleep monitor data were scored by a central Sleep Reading Center (Case Western Reserve University/Brigham and Women’s Hospital). Respiratory events were defined as a 50% or more reduction in airflow lasting at least 10 seconds. Apneas were not distinguished from hypopneas as thermistry was not available. Each respiratory event was manually identified and linked to its level of desaturation, and artifact was manually edited on an epoch-by-epoch basis. The current analyses used the 3% desaturation variable in accordance with current recommended
scoring criteria from the American Academy of Sleep Medicine. The majority of the sleep studies (over 80%) included in the analyses had at least 4 hours of total recording time. The AHI obtained from the monitoring device has been shown to have excellent correlation with AHI obtained from in-lab attended sleep testing. Clinically significant SA was defined as an AHI ≥15 per hour (associated with a 3% desaturation). Mild SA was defined as an AHI ≥ 5 and < 15, moderate SA as AHI ≥ 15 and < 30, and severe SA as AHI ≥ 30/hr. Inter- and–intra scorer reliability estimates for the AHI, assessed over the course of the study, were excellent (intraclass correlation coefficients > 0.99).

Covariates

Obesity was defined based on measured weight and height as a body-mass index (BMI) ≥ 30 kg/m². Waist and hip were measured and used to compute the waist-to-hip ratio, which was used as a marker of central adiposity. Hypertension was defined using recommendations from the Joint National Committee as a blood pressure ≥140/90 mm Hg or a medication review revealing use of antihypertensive. Diabetes was defined according to recommendations from the American Diabetes Association as a fasting glucose ≥126 mg/ml or an abnormal oral glucose tolerance test (post-OGTT glucose ≥200 mg/ml) or an abnormal hemoglobin A1C (≥6.5%). We also included in the definition of diabetes any use of prescription drugs for diabetes. Dyslipidemia was defined as a total cholesterol/high-density lipoprotein cholesterol level > 5 or use of a cholesterol lowering medication.

Cigarette use was defined using pack-years of smoking with a 3-level categorical variable defined as “never”, “0-10” pack-years, and “10 and plus” pack-years; cigarette pack years was calculated as the number of exposure years multiplied by the average number of cigarettes smoked per day and divided by 20. Alcohol use was defined as “never”, “former” or “current” based on self-report. Physical activity was assessed using the Global Physical Activity Questionnaire (GPAQ). A dichotomous variable (yes/no) for physical activity was created based on whether or not the participant met the 2008 Physical Activity Guidelines for Americans.

Prevalent coronary heart disease (CHD) was defined using a variable that combined ECG reports obtained at baseline that suggested the presence of possible old myocardial infarction, as well as self-reported diagnosis of angina, “heart attack” or cardiac procedures, i.e. angioplasty, stent or coronary artery bypass graft surgery.

Statistical Analysis

Student’s t-test and the chi-square test (as appropriate) were used to compare values of characteristics at baseline for participants with and without PAD. We used multivariable logistic regression to assess the association between SA and PAD. Secondary analyses examined the association of PAD with other sleep variables including T90 (amount of recording time spent with an oxygen saturation less than 90%) or lowest oxygen saturation during the sleep period. All models were adjusted for age, sex, BMI, waist hip ratio, hypertension, CHD, diabetes, dyslipidemia, high sensitivity C-reactive protein (CRP) levels, smoking, alcohol use, physical activity, study site, and Hispanic/Latino background. Finally, differences between men and women and among the different Hispanic/Latino backgrounds in the observed associations were evaluated by testing the interaction with a more conservative significance level (0.01). Primary analyses were interpreted as statistically significant if p < 0.05. All analyses accounted for the complex survey design and sampling weights, were conducted by HCHS/SOL coordinating center (University of North Carolina – Chapel Hill) and performed using SAS 9.3 software (SAS Institute, Cary, NC) and SUDAAN software Release 11 (RTI International, Research Triangle Park, NC). The multi-stage sampling design and cohort
selection procedures have been described elsewhere in detail.  
Briefly, participants were recruited from defined geographical areas selected to provide a representative sample of the target population and diversity among participants with regard to socioeconomic status and national origin or background. Of individuals who were screened and selected and who met eligibility criteria, 41.7% were enrolled, representing 16,415 persons from 9,872 households.

References