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Title

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Permalink

<https://escholarship.org/uc/item/3774s2ts>

Journal

Arteriosclerosis, thrombosis, and vascular biology, 35(3)

ISSN

1079-5642

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Publication Date

2015-03-01

DOI

10.1161/atvbaha.114.304625

Peer reviewed



Published in final edited form as:

Arterioscler Thromb Vasc Biol. 2015 March ; 35(3): 710–715. doi:10.1161/ATVBAHA.114.304625.

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

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Abstract

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 (ABI). This relationship was evaluated in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).

Approach and Results—We studied 8,367 HCHS/SOL 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 ABI. PAD was defined as ABI < 0.90 in either leg. Multivariable logistic regression was utilized to investigate the association between moderate-to-severe SA, defined as apnea-hypopnea index (AHI) ≥ 15 , and the presence of PAD. Analyses were adjusted for covariates.

The prevalence of PAD was 4.7% (n=390). The mean AHI was significantly higher among adults with PAD compared to those without (11.1 vs. 8.6 events/hour, p=0.046). After adjusting for

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Disclosures
None

covariates, moderate-to-severe SA was associated with a 70% increase in the odds of PAD (odds ratio 1.7, 95% CI: 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 OR 2.9, 95% CI: 1.3, 6.2) and in Puerto Rican Americans (adjusted OR 2.0, 95% CI: 0.97 – 4.2) than in other backgrounds.

Conclusions—Moderate-to-severe SA is associated with higher odds of PAD in Hispanic/Latino adults.

Keywords

Sleep apnea; peripheral arterial disease; ankle-brachial index; subclinical atherosclerosis; US Hispanics and Latinos

Introduction

We recently reported the prevalence of mild, moderate and severe sleep apnea (SA) in the U.S. 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.⁵ Numerous studies^{5–22} have explored the relationship between SA and measures of atherosclerotic vascular disease in clinical or population-based samples. Such studies have examined the endpoint 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 PAD among participants enrolled in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). 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 HCHS/SOL participants, those younger than 45 years of age were not assessed for ABI, resulting in exclusion of 6,710 participants. Of the remaining participants, 1,110 (6.76%) had missing or incomplete SA data, 39 (0.24%) 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 8,367 individuals.

The overall prevalence of PAD was 4.7% (n=390). Compared to those without PAD, participants with PAD were older (mean age 61 vs. 56 years, $p<0.0001$) and more often women (67% vs. 55%; $p=0.0001$) (Table 1). The mean BMI was not significantly different between the two groups. As expected, the prevalence of comorbidities such as hypertension, CHD and diabetes were higher in the PAD group compared to the non-PAD group. Similarly, 10 and more pack-years of smoking history was more common in the group with PAD (39% vs. 24%).

The mean AHI was significantly higher among adults with PAD compared to those without PAD (11.1 vs. 8.6 events/hour, $p=0.046$) (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 less than 90% between the two groups (data not shown).

Table 2 shows the odds ratios (OR) from the multivariable model assessing the relationship between no to mild SA and moderate to severe SA (AHI 15) to PAD. After adjusting for age, sex, BMI, waist hip ratio, hypertension, CHD, diabetes, dyslipidemia, CRP levels, smoking, alcohol use, physical activity, study site, and Hispanic/Latino background, individuals with moderate-to-severe SA were 1.67 (95% 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 5–15 events/hour, 15–30 events/hour and > 30 events/hour. In an adjusted model, AHI 15–30 (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 confidence interval (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 CRP 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, BMI, waist hip ratio, hypertension, CHD, diabetes, dyslipidemia, CRP levels, smoking, alcohol use, physical activity, study site, and Hispanic/Latino background. The magnitude of this association was not modified by sex. Further, 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 hypertension²⁶, coronary heart disease^{4,27}, cardiac arrhythmias²⁸, heart failure^{29,30}, stroke³¹ and sudden death.³² Plausible mechanisms that may contribute to an overall increased vascular risk in the setting of OSA include dyslipidemia³³, glucose intolerance³⁴, diabetes³⁵, sympathetic activation³⁶, systemic inflammation^{37,38}, endothelial dysfunction^{19,39}, oxidative stress⁴⁰, and autonomic dysfunction.⁴¹ Our study contributes to the literature linking SA with subclinical markers of vascular disease risk, which include several prior studies of the coronary and cerebrovascular beds.^{6,12,18,21,42} SA is associated with increased carotid artery atherosclerosis and treatment of SA appears 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 non-invasively.⁴⁶⁻⁴⁸ However, until the present study similar evidence for the association between SA and PAD was lacking.

PAD affects approximately 20% of individuals older than 60 years and can cause disabling symptoms due to claudication.⁴⁹ PAD is a marker of underlying atherosclerosis severity and prognosis, which shares many risk factors with SA including hypertension, obesity and diabetes.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 use of the ABI, a non-invasive, 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 to other non-invasive measures of atherosclerosis, typically requires more extensive burden of disease.

The HCHS/SOL assessed SA with an in-home sleep study as opposed to in-lab 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 REM sleep was not adequately represented. However, we found no association between recording time and either AHI or ABI (data not shown). Further, 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 coronary heart disease (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 sleep apnea on different vascular beds, i.e. coronary vs. peripheral.

Future work is recommended to understand whether sleep apnea 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 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 due to the sample size limitations, which may be clarified in future studies about dose-response relationships.

Finally, we noted that Hispanic/Latino group appears to modify the relationship between SA and PAD, with stronger effects for Mexicans and Puerto Ricans relative to other backgrounds (listed in Table 1). In our sample, Puerto Ricans had the highest prevalence of obesity (50.2%, S.E. 2.32) when compared to 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.⁵⁴ 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.⁵⁵ Prior studies evaluating the association between SA and subclinical peripheral atherosclerosis have not utilized 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 multi-center National Institutes of Health-sponsored cohort study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the staff and participants of HCHS/SOL for their important contributions.

Sources of Funding: The Hispanic Community Health Study/Study of Latinos was carried out as a collaborative study supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (N01-HC65233), University of Miami (N01-HC65234), Albert Einstein College of Medicine (N01-HC65235), Northwestern University (N01-HC65236), and San Diego State University (N01-HC65237). The following Institutes/Centers/Offices contribute to the HCHS/SOL through a transfer of funds to the NHLBI: National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, National Institutes of Health Institution-Office of Dietary Supplements.

Abbreviations

SA	Sleep apnea
PAD	Peripheral arterial disease
ABI	Ankle- brachial index
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
AHI	Apnea–hypopnea index
BMI	Body Mass Index
CHD	Coronary Heart Disease
OR	Odds ratio
CI	Confidence Interval

References

1. Redline S, Sotres-Alvarez D, Loredo J, Hall M, Patel SR, Ramos A, Shah N, Ries A, Arens R, Barnhart J, Youngblood M, Zee P, Daviglius ML. Sleep-disordered Breathing in Hispanic/Latino Individuals of Diverse Backgrounds. The Hispanic Community Health Study/Study of Latinos. *Am J Respir Crit Care Med.* 2014; 189:335–344. [PubMed: 24392863]
2. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet.* 2005; 365:1046–53. [PubMed: 15781100]
3. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med.* 2005; 353:2034–41. [PubMed: 16282178]
4. Shah NA, Yaggi HK, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. *Sleep Breath.* 2010; 14:131–136. [PubMed: 19777281]
5. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2005; 172:613–618. [PubMed: 15901608]
6. Arik B, Inci MF, Gumus C, Varol K, Ege MR, Dogan OT, Zorlu A. Advanced age and apnea-hypopnea index predict subclinical atherosclerosis in patients with obstructive sleep apnea syndrome. *Multidiscip Respir Med.* 2013; 8 9-6958-8-9.
7. Drager LF, Bortolotto LA, Krieger EM, Lorenzi-Filho G. Additive effects of obstructive sleep apnea and hypertension on early markers of carotid atherosclerosis. *Hypertension.* 2009; 53:64–69. [PubMed: 19015401]

8. Nagahama H, Soejima M, Uenomachi H, Higashi Y, Yotsumoto K, Samukawa T, Arima T. Pulse wave velocity as an indicator of atherosclerosis in obstructive sleep apnea syndrome patients. *Intern Med.* 2004; 43:184–188. [PubMed: 15098597]
9. Hayashi M, Fujimoto K, Urushibata K, Uchikawa S, Imamura H, Kubo K. Nocturnal oxygen desaturation correlates with the severity of coronary atherosclerosis in coronary artery disease. *Chest.* 2003; 124:936–941. [PubMed: 12970020]
10. Wattanakit K, Boland L, Punjabi NM, Shahar E. Relation of sleep-disordered breathing to carotid plaque and intima-media thickness. *Atherosclerosis.* 2008; 197:125–131. [PubMed: 17433330]
11. Tanriverdi H, Evrengul H, Kara CO, Kuru O, Tanriverdi S, Ozkurt S, Kaftan A, Kilic M. Aortic stiffness, flow-mediated dilatation and carotid intima-media thickness in obstructive sleep apnea: non-invasive indicators of atherosclerosis. *Respiration.* 2006; 73:741–750. [PubMed: 16717439]
12. Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Tanaka A, Oda N, Okada S, Ohta S, Naito H, Adachi M. Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2005; 172:625–630. [PubMed: 16120716]
13. Suzuki T, Nakano H, Maekawa J, Okamoto Y, Ohnishi Y, Yamauchi M, Kimura H. Obstructive sleep apnea and carotid-artery intima-media thickness. *Sleep.* 2004; 27:129–133. [PubMed: 14998249]
14. Drager LF, Bortolotto LA, Maki-Nunes C, Trombetta IC, Alves MJ, Fraga RF, Negrao CE, Krieger EM, Lorenzi-Filho G. The incremental role of obstructive sleep apnoea on markers of atherosclerosis in patients with metabolic syndrome. *Atherosclerosis.* 2010; 208:490–495. [PubMed: 19762024]
15. Tsuda H, Almeida FR, Tsuda T, Moritsuchi Y, Lowe AA. Cephalometric calcified carotid artery atheromas in patients with obstructive sleep apnea. *Sleep Breath.* 2010; 14:365–370. [PubMed: 20084549]
16. Szaboova E, Tomori Z, Donic V, Petrovicova J, Szabo P. Sleep apnoea inducing hypoxemia is associated with early signs of carotid atherosclerosis in males. *Respir Physiol Neurobiol.* 2007; 155:121–127. [PubMed: 16790368]
17. Altin R, Ozdemir H, Mahmutyazicioglu K, Kart L, Uzun L, Ozer T, Savranlar A, Aydin M. Evaluation of carotid artery wall thickness with high-resolution sonography in obstructive sleep apnea syndrome. *J Clin Ultrasound.* 2005; 33:80–86. [PubMed: 15674835]
18. Tian JL, Zhang Y, Wang Z, Cao L, Chen BY. A study on non-invasive indexes of atherosclerosis in obstructive sleep apnea-hypopnea syndrome patients. *Zhonghua Jie He He Hu Xi Za Zhi.* 2006; 29:395–398. [PubMed: 17045022]
19. Faulx MD, Larkin EK, Hoit BD, Aylor JE, Wright AT, Redline S. Sex influences endothelial function in sleep-disordered breathing. *Sleep.* 2004; 27:1113–1120. [PubMed: 15532205]
20. Chami HA, Keyes MJ, Vita JA, Mitchell GF, Larson MG, Fan S, Vasan RS, O'Connor GT, Benjamin EJ, Gottlieb DJ. Brachial artery diameter, blood flow and flow-mediated dilation in sleep-disordered breathing. *Vasc Med.* 2009; 14:351–360. [PubMed: 19808720]
21. Ciccone MM, Scicchitano P, Mitacchione G, Zito A, Gesualdo M, Caputo P, Damiani MF, Sassara M, Favale S, Resta O, Carratu P. Is there a correlation between OSAS duration/severity and carotid intima-media thickness? *Respir Med.* 2012; 106:740–746. [PubMed: 22317765]
22. Drager LF, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: an emerging risk factor for atherosclerosis. *Chest.* 2011; 140:534–542. [PubMed: 21813534]
23. Silvestrini M, Rizzato B, Placidi F, Baruffaldi R, Bianconi A, Diomedes M. Carotid artery wall thickness in patients with obstructive sleep apnea syndrome. *Stroke.* 2002; 33:1782–5. [PubMed: 12105352]
24. Friedlander AH, Yueh R, Littner MR. The prevalence of calcified carotid artery atheromas in patients with obstructive sleep apnea syndrome. *Journal of Oral & Maxillofacial Surgery.* 1998; 56:950–4. [PubMed: 9710189]
25. Hanssen NM, Huijberts MS, Schalkwijk CG, Nijpels G, Dekker JM, Stehouwer CD. Associations between the ankle-brachial index and cardiovascular and all-cause mortality are similar in individuals without and with type 2 diabetes: nineteen-year follow-up of a population-based cohort study. *Diabetes Care.* 2012; 35:1731–1735. [PubMed: 22699294]

26. Peppard P, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med.* 2000; 342:1378–84. [PubMed: 10805822]
27. Peker Y, Kraiczi H, Hedner J, Loth S, Johansson A, Bende M. An independent association between obstructive sleep apnoea and coronary artery disease. *Eur Respir J.* 1999; 14:179–184. [PubMed: 10489848]
28. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S, Sleep Heart Health Study. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. *Am J Respir Crit Care Med.* 2006; 173:910–916. [PubMed: 16424443]
29. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation.* 2010; 122:352–360. [PubMed: 20625114]
30. Shahar E, Whitney C, Redline S, Lee E, Newman A, Javier Nieto F, O'Connor G, Boland L, Schwartz J, Samet J. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med.* 2001; 163:19–25. [PubMed: 11208620]
31. Yaggi H, Brass L, Kernan W, Lichtman J, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke. *Stroke.* 2004; 316:365.
32. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med.* 2005; 352:1206–14. [PubMed: 15788497]
33. Arsenault BJ, Boekholdt SM, Kastelein JJ. Lipid parameters for measuring risk of cardiovascular disease. *Nat Rev Cardiol.* 2011; 8:197–206. [PubMed: 21283149]
34. Punjabi NM, Sorkin JD, Katzell LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med.* 2002; 165:677–82. [PubMed: 11874813]
35. Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK. Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med.* 2009; 122:1122–1127. [PubMed: 19958890]
36. Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, Skatrud J. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med.* 1997; 157:1746–1752. [PubMed: 9250236]
37. Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, Hirano T, Adachi M. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation.* 2003; 107:1129–34. [PubMed: 12615790]
38. Kapsimalis F, Varouchakis G, Manousaki A, Daskas S, Nikita D, Kryger M, Gourgoulis K. Association of sleep apnea severity and obesity with insulin resistance, C-reactive protein, and leptin levels in male patients with obstructive sleep apnea. *Lung.* 2008; 186:209–217. [PubMed: 18365276]
39. Nieto FJ, Herrington DM, Redline S, Benjamin EJ, Robbins JA. Sleep apnea and markers of vascular endothelial function in a large community sample of older adults. *Am J Respir Crit Care Med.* 2004; 169:354–360. [PubMed: 14551166]
40. Lavie L. Obstructive sleep apnoea syndrome—an oxidative stress disorder. *Sleep Med Rev.* 2003; 7:35–51. [PubMed: 12586529]
41. Narkiewicz K, Somers VK. Cardiovascular variability characteristics in obstructive sleep apnea. *Auton Neurosci.* 2001; 90:89–94. [PubMed: 11485297]
42. Baguet JP, Hammer L, Levy P, Pierre H, Launois S, Mallion JM, Pepin JL. The severity of oxygen desaturation is predictive of carotid wall thickening and plaque occurrence. *Chest.* 2005; 128:3407–12. [PubMed: 16304292]
43. Hui DS, Shang Q, Ko FW, Ng SS, Szeto CC, Ngai J, Tung AH, To KW, Chan TO, Yu CM. A prospective cohort study of the long-term effects of CPAP on carotid artery intima-media thickness in obstructive sleep apnea syndrome. *Respir Res.* 2012; 13 22-9921-13-22.

44. Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi GF. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2007; 176:706–712. [PubMed: 17556718]
45. Kylintireas I, Craig S, Nethononda R, Kohler M, Francis J, Choudhury R, Stradling J, Neubauer S. Atherosclerosis and arterial stiffness in obstructive sleep apnea—a cardiovascular magnetic resonance study. *Atherosclerosis.* 2012; 222:483–489. [PubMed: 22560328]
46. Kent BD, Garvey JF, Ryan S, Nolan G, Dodd JD, McNicholas WT. Severity of obstructive sleep apnoea predicts coronary artery plaque burden: a coronary computed tomographic angiography study. *Eur Respir J.* 2013; 42:1263–1270. [PubMed: 23471346]
47. Sharma S, Gebregziabher M, Parker AT, Abro JA, Armstrong AM, Schoepf UJ. Independent association between obstructive sleep apnea and noncalcified coronary plaque demonstrated by noninvasive coronary computed tomography angiography. *Clin Cardiol.* 2012; 35:641–645. [PubMed: 22949086]
48. Tan A, Hau W, Ho HH, Ghaem Maralani H, Loo G, Khoo SM, Tai BC, Richards AM, Ong P, Lee CH. OSA and coronary plaque characteristics. *Chest.* 2014; 145:322–330. [PubMed: 24178625]
49. Criqui MH, Fronck A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation.* 1985; 71:510–515. [PubMed: 3156006]
50. Heald CL, Fowkes FG, Murray GD, Price JF, Ankle Brachial Index Collaboration. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: Systematic review. *Atherosclerosis.* 2006; 189:61–69. [PubMed: 16620828]
51. Hirsch AT, Haskal ZJ, Hertzner NR, et al. American Association for Vascular Surgery, Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, ACC/AHA Task Force on Practice Guidelines Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease, American Association of Cardiovascular and Pulmonary Rehabilitation, National Heart, Lung, and Blood Institute, Society for Vascular Nursing, TransAtlantic Inter-Society Consensus, Vascular Disease Foundation. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation.* 2006; 113:e463–654. [PubMed: 16549646]
52. Mohler E 3rd, Giri J ACC, AHA. Management of peripheral arterial disease patients: comparing the ACC/AHA and TASC-II guidelines. *Curr Med Res Opin.* 2008; 24:2509–2522. [PubMed: 18664318]
53. Utriainen KT, Airaksinen JK, Polo O, Raitakari OT, Pietila MJ, Scheinin H, Helenius HY, Leino KA, Kentala ES, Jalonen JR, Hakovirta H, Salo TM, Laitio TT. Unrecognised obstructive sleep apnoea is common in severe peripheral arterial disease. *Eur Respir J.* 2013; 41:616–620. [PubMed: 22700841]
54. Punjabi NM, Beamer BA. C-reactive protein is associated with sleep disordered breathing independent of adiposity. *Sleep.* 2007; 30:29–34. [PubMed: 17310862]
55. Redline S, Sotres-Alvarez D, Loreda J, Hall M, Patel SR, Ramos A, Shah N, Ries A, Arens R, Barnhart J, Youngblood M, Zee P, Daviglius ML. Sleep-disordered breathing in Hispanic/Latino individuals of diverse backgrounds. The Hispanic Community Health Study/Study of Latinos. *Am J Respir Crit Care Med.* 2014; 189:335–344. [PubMed: 24392863]

Significance

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 American 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, BMI, waist hip ratio, hypertension, CHD, diabetes, dyslipidemia, CRP 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 PAD improves with SA treatment. Further research may assess whether SA variably influences the atherosclerotic process in different vascular beds.

Table 1

Characteristics of the Study Sample Based on PAD Status

Characteristic	PAD absent (N=7977)	PAD present (N=390)	P-value
Age, years	56.0 (0.15)	60.7 (0.68)	<0.0001
Females, %	54.7 (0.74)	67.4 (3.00)	<0.0001
BMI, kg per m ²	29.8 (0.09)	29.7 (0.46)	0.7800
Waist Circumference, cm	99.6 (0.21)	99.5 (1.01)	0.8597
Mean Waist to Hip Ratio	0.94 (0.00)	0.94 (0.00)	0.9063
Hypertension, %	41.3 (0.99)	63.9 (3.19)	<0.0001
Prevalent CHD, %	9.44 (0.54)	18.3 (2.82)	0.0058
Diabetes, %	26.5 (0.79)	44.7 (3.40)	<0.0001
Dyslipidemia, %	44.3 (0.85)	50.1 (3.66)	0.1218
Meet 2008 PA guidelines, %	58.9 (0.91)	51.0 (3.29)	0.0230
Mean log hsCRP Level	0.64 (0.02)	0.94 (0.07)	<0.0001
Cigarette Pack-Years, %			0.0014
Never Smoking	56.5 (0.90)	41.8 (3.76)	
0–10	18.3 (0.76)	18.1 (2.79)	
10 and plus	24.2 (0.89)	39.2 (3.88)	
Alcohol use, %			.0052
Never	21.4 (0.88)	32.5 (3.76)	
Former	33.6 (0.92)	33.8 (3.47)	
Current	45.0 (0.86)	33.7 (3.28)	
Hispanic/Latino Background, %			
Dominican	9.5 (0.77)	6.9 (1.51)	<0.0001
Central American	6.5 (0.43)	7.2 (1.48)	
Cuban	24.1 (1.95)	40.0 (4.22)	
Mexican Puerto Rican	34.0 (1.77)	17.9 (3.22)	
South American	5.43 (0.37)	5.0 (1.19)	
More than one/Other	2.27 (0.36)	2.54 (0.96)	
AHI, events/hour	8.63 (0.23)	11.14 (1.25)	0.0466
Mean Lowest Oxygen Saturation (Minimum SpO ₂)	85.8 (0.12)	84.1 (0.62)	0.0062
Epworth Sleepiness Scale	5.9 (0.09)	5.7 (0.39)	0.6399

All values are weighted to account for the complex survey design. Standard errors in parenthesis.

PAD: Peripheral arterial disease; BMI: Body mass index; AHI: Apnea hypopnea index; CHD: coronary heart disease; PA: physical activity; hsCRP: highly sensitive C-reactive protein

Table 2

Multivariable model assessing the relationship of moderate to severe SA (AHI ≥ 15) and other clinical factors with PAD

Characteristic	Odds Ratio	95% Confidence Interval	P-value
Age (per year)	1.03	1.01–1.06	0.0144
Male (vs. female)	0.40	0.28–0.56	<0.0001
BMI (per unit)	0.93	0.89–0.96	0.0001
Waist hip ratio (per unit)	2.44	0.26–23.05	0.4372
Hypertension	1.58	1.10–2.26	0.0123
CHD	1.50	1.01–2.22	0.0465
Diabetes	1.60	1.05–2.45	0.0287
Dyslipidemia	0.93	0.67–1.29	0.6694
hsCRP (per mg/L)	1.12	1.04–1.19	0.0013
Pack-year of smoking: Less than 10 vs. Never	1.57	1.03–2.39	0.0341
Pack-year of smoking: 10+ vs Never	2.34	1.47–3.72	0.0003
Alcohol: Former vs. Never	1.00	0.59–1.68	0.9969
Alcohol: Current vs. Never	0.89	0.57–1.40	0.6083
Meet 2008 PA guidelines	1.05	0.77–1.43	0.7651
Moderate-to-severe SA (AHI ≥ 15 , vs. AHI<15)	1.67	1.10–2.51	0.0152

Odds ratios are adjusted for all variables listed plus study site and Hispanic/Latino background.

SA: Sleep apnea; AHI: Apnea hypopnea index; PAD: Peripheral arterial disease; BMI: Body mass index; CHD: Coronary heart disease; hsCRP: highly sensitive C-reactive protein; PA: physical activity.

Table 3

Relationship between Severity of SA and PAD

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

Odds ratio is adjusted for: age, sex, study site, Hispanic/Latino background, education, income, BMI, pack years smoking, hypertension, CHD, diabetes, dyslipidemia, waist hip ratio, physical activity and hsCRP

SA: Sleep apnea; PAD: Peripheral arterial disease; AHI: Apnea hypopnea index; BMI: Body mass index; CHD: coronary heart disease; hsCRP: highly sensitive C-reactive protein