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Obstructive Sleep Apnea is Associated with Future Subclinical Carotid Artery Disease: Thirteen-Year Follow-up from the Wisconsin Sleep Cohort

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Abstract

Objective—To determine the longitudinal associations between obstructive sleep apnea (OSA), carotid artery intima-media thickness (IMT), and plaque.

Approach and Results—This is a population-based, prospective cohort study conducted from July, 1989 to November, 2012 on 790 randomly selected employed Wisconsin residents who completed a mean of 3.5 (range 1–6) polysomnograms during the study period. OSA was characterized by the apnea-hypopnea index (AHI, events/hour). Common carotid artery IMT and plaque were assessed by B-mode ultrasound. The mean (SD) time from the first polysomnograms to carotid ultrasound was 13.5 (3.6) years. Multivariable regression models were created to estimate the independent associations of baseline and cumulative OSA exposure with subsequent carotid IMT and plaque. At baseline, participants were mean 47.6 (7.7) years old (55% male, 97% white). AHI was 4.4 (9.0) events/hour (range, 0–97); 7% had AHI>15 events/hour. Carotid IMT was 0.755 (0.161) mm; 63% had plaque. Adjusting for age, sex, body-mass index, systolic blood pressure, smoking, and use of lipid-lowering, antihypertensive, and diabetes medications, baseline AHI independently predicted future carotid IMT (β=0.027 mm/unit $\log_{10}$[AHI+1], p=0.049), plaque presence (odds ratio 1.55 [95% confidence intervals 1.02–2.35], p=0.041) and plaque score (odds ratio 1.30 [1.05–1.61], p=0.018). In cumulative risk factor-adjusted models, AHI independently predicted future carotid plaque presence (p=0.012) and score (p=0.039), but not IMT (p=0.608).

Conclusions—Prevalent OSA is independently associated with increased carotid IMT and plaque over a decade later, indicating increased future cardiovascular disease risk.

Keywords

Atherosclerosis; Carotid arteries; Epidemiology; Sleep apnea; Ultrasound; Sleep disorders

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Introduction

Obstructive sleep apnea (OSA) is associated with increased risk of cardiovascular disease (CVD) and all-cause mortality.[1–4] OSA is characterized by repeated episodes of airway obstruction with a concomitant decrease in oxygen saturation, increased ventilatory effort, and nocturnal arousals.[4] Repetitive hypoxic insults and exaggerated fluctuations in intra-thoracic pressure associated with OSA alter cardiovascular hemodynamics and may lead to endothelial dysfunction, vascular inflammation and sympathetic activation that are thought to be associated with the initiation and progression of atherosclerosis.[5–7] OSA has become an important public health concern due to its rising prevalence, likely related to the epidemic of obesity.[8,9] Because OSA is strongly associated with obesity and visceral adiposity, its independent effects on atherosclerosis and CVD risk are not clear.

Increased carotid artery intima-media thickness (IMT) and carotid artery plaque presence are markers of subclinical arterial disease that predict future CVD events.[10–16] Current evidence for the association between OSA and carotid IMT is limited and based on results from cross-sectional and case-control studies.[17–25] The few studies that examined associations of the duration and severity of OSA with carotid IMT and plaque were limited by small sample sizes, short duration of follow-up, and/or retrospective ascertainment of OSA duration using questionnaires. A recent meta-analysis of 16 studies concluded that subjects with OSA had higher carotid IMT, but noted that the existing data are of low-quality.[26]

The objective of this study was to evaluate the long-term associations of measures of baseline and cumulative OSA with carotid IMT and plaque using data from the Wisconsin Sleep Cohort Study, a large longitudinal study of the natural history of OSA in adults. We hypothesized that more severe OSA would predict increased future carotid IMT and a greater burden of carotid plaque, and that these associations would persist even after adjusting for body-mass index and other CVD risk factors.

Materials and Methods

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

Results

Demographics

At baseline, the mean (standard deviation) age of the 790 participants was 47.6 (7.7) years old (56% male, 97% white) (Table 1). Mean body-mass index was 29.6 (6.0) kg/m^2; 13% of participants were taking anti-hypertensive medications, and 16% were smokers. At the carotid IMT assessment visit (mean 13.5 [3.6] years later) the participants mean age was 61.1 (7.7) years; mean body-mass index had increased to 31.2 (7.1) kg/m^2 and 47% were taking anti-hypertensive medications. The mean-mean carotid IMT was 0.755 (0.161) mm; 63% had carotid plaque with an average carotid plaque score of 2.1 (2.4). The weighted mean serum glucose was 100 (20) mg/dL and weighted mean high-density lipoprotein cholesterol was 49 (13) mg/dL.

Associations between Baseline AHI and Future IMT and Plaque Burden

Table 2 shows the associations between baseline AHI and future carotid IMT, plaque presence and plaque score after adjusting for age, sex, body-mass index, systolic blood pressure, current smoking, and use of anti-hypertensive-, anti-diabetic- and lipid-lowering medications. Baseline AHI was an independent predictor of increased carotid IMT (β=0.027 mm/unit logAHI; p=0.049). Baseline AHI also predicted future plaque presence (OR 1.55 [95% CI 1.02–2.35], p=0.041) and future plaque score (OR 1.30 [95% CI 1.05–1.61], p=0.018). Covariates that consistently predicted future carotid IMT, plaque presence and plaque score in the baseline AHI models included age, systolic blood pressure and current smoking (Supplementary Tables IA, IIA and IIIA). Use of lipid-lowering and anti-diabetic medications predicted future IMT, but not plaque burden. Neither exercise intensity nor shift work were significant predictors of IMT or plaques. Adding shift work or exercise or both to the baseline models had no or minimal effects on the beta coefficients, odds ratios and p-values (data not shown).

Models including CPAP users were not created because only seven subjects were treated with CPAP at baseline. Cumulative AHI models with and without CPAP users showed similar results. To investigate possible risk factor modification of the effects of AHI on the outcome variables, we added interaction terms for age, sex, smoking and BMI to the models. None of these had significant interactions with AHI (data not shown). In categorical models, AHI (i.e. 0–5, 5–15, >15 and CPAP user), the AHI 5–15 category was significantly associated with future IMT (β=0.033 mm/unit logAHI; p=0.037). No other AHI category was related significantly to IMT or plaques.

Associations between AUC-AHI and Future IMT and Plaque Burden

AUC-AHI predicted increased carotid IMT after adjusting for age and sex (β=0.0027 mm/unit AUC-AHI; p=0.001), but this association no longer was significant when weighted mean body-mass index was included (Supplemental Table IB). In the fully-adjusted model, AUC-AHI was not a significant predictor of future carotid IMT (Table 2). However, AUC-AHI predicted both future carotid plaque presence (OR 1.037 [95% CI 1.008–1.066], p=0.012) and plaque score (OR 1.013 [95% CI 1.001–1.026], p=0.039) after adjusting for all covariates. Covariates that consistently predicted future carotid IMT, plaque presence and plaque score in the AUC-AHI models included age, weighted systolic blood pressure, pack-years of smoking and mean high-density lipoprotein cholesterol (Supplementary Tables IB, IIB and IIIB). Models excluding CPAP users showed similar results for IMT (β=0.0054 mm/unit AUC-AHI; p=0567), plaque presence (OR 1.046 [95% CI 1.014–1.080], p=0.004) and plaque score (OR 1.015 [95% CI 1.001–1.029], p=0.038). As for the baseline AHI models, neither shift work nor exercise predicted future IMT or plaques or significantly changed the beta coefficients or odds ratios for AUC-AHI. Similarly, neither age, gender, smoking nor BMI interacted with AUC-AHI to predict the outcome variables. Because AUC-AHI could not logically be transformed to the classic AHI categories we added quadratic AUC-AHI to the models. The quadratic term was not statistically significant (data not shown).

Discussion

This the first large (n=790) longitudinal cohort study to show that baseline AHI is an independent predictor of increased carotid IMT and carotid plaques, over more than a decade later. Furthermore, cumulative OSA exposure measured as repeated AHI over time is associated with future carotid plaque burden after adjusting for traditional CVD risk factors such as hypertension, diabetes mellitus and smoking. These novel findings have important preventive implications because of the increasing prevalence of OSA in the United States[8] and also because carotid IMT and plaques are surrogate markers of atherosclerosis that predict incident stroke,[10,16] and coronary heart disease.[11–16]

Previous data on the association between OSA and IMT was based mostly on small (<100 participant) cross-sectional studies. A recent systematic review of these studies showed that patients with OSA had increased IMT compared to controls.[27] Similarly, case-control studies have demonstrated a positive association between OSA and plaques.[18,20] Because most patients with OSA have other risk factors for CVD and are obese, it has been challenging to establish a causal relationship between OSA and atherosclerosis. In a small study, 24 patients with severe OSA were randomized to 4 months of CPAP treatment versus no treatment.[23] They found a significant reduction in IMT in the treatment group.[23] A positive association between OSA and IMT was identified in 156 patients with severe OSA, but a major limitation of that study was retrospective assessment of OSA duration.[25] One study, however, did not observe an association between OSA and carotid IMT after adjusting for covariates in subjects recruited from the general community, [21] however in almost half of the cases, measurements of carotid artery and covariates were performed before the sleep studies.

Another major finding of the current investigation is that baseline AHI was associated with both future carotid IMT and plaques, but the cumulative AHI only was associated with future plaques. A possible explanation for this difference is that BMI is more strongly correlated with common carotid artery medial hypertrophy and therefore IMT than with plaques, as supported by our observation that the cumulative-AHI association with IMT was rendered insignificant by the addition of weighted BMI. This suggests that AHI is, in general, a stronger predictor of carotid plaques than IMT. This observation has important clinical implications because carotid plaques appear to be stronger predictors of future CVD risk than carotid IMT.[14]

In contrast to previous studies that have shown shift-work to be related to subclinical atherosclerosis,[28] we did not find an association between AHI and future IMT. We also evaluated possible effects of exercise and the interaction of AHI and age, gender, smoking and BMI. None of these aforementioned variables had significant effect on the associations between AHI and IMT which further suggest that AHI is a robust independent predictor of the carotid measurements. We examined the associations of categorical AHI with IMT and plaques and found no “cut-off” points.

Limitations

Our cohort was 97% Caucasian which may limit the generalizability of our findings. Our participants were recruited from a working, non-clinical population, so we had relatively few participants with severe OSA (e.g., AHI>30 events/hr). Because we did not have baseline carotid artery measurements, we could not carotid IMT progression. Nevertheless, we found robust, longitudinal associations between increasing AHI and the carotid ultrasound measures. We did not include measurements of nocturnal oxygen saturation in our models since the aim of the study was to focus on baseline and cumulative AHI. Nocturnal oxygen saturation parameters are subject of future analysis. The estimated cumulative OSA exposure was based on the time of the OSA diagnosis, however some participants were undiagnosed for an known period of time. This however, would be expected to lead to a null bias. We did not have measurements of inflammatory markers, markers of oxidative stress or cathecholamines and thus, could not investigate the pathophysiological pathways that have been proposed for the connection between OSA and atherosclerosis. Additionally, we did not have serum glucose, total cholesterol, or high-density lipoprotein cholesterol levels at baseline so we were unable to control for baseline levels of those factors. However, high-density lipoprotein cholesterol and glucose were included in our AUC-AHI models. As with all observational studies, failure to fully account for all important confounding factors may have led to misestimated associations of interest.

Conclusions

Prevalent OSA independently predicts future carotid IMT, carotid plaque presence, and carotid plaque burden. The longitudinal association of OSA with carotid IMT is confounded by increasing body-mass index and mediated by traditional CVD risk factors; however chronic exposure to OSA is independently related to carotid plaque presence and burden. Our results demonstrate a physiological connection between OSA and carotid atherosclerosis and underscore the importance of early diagnosis and treatment of OSA to reduce future CVD risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conception and design of the study: PEP, TY, KMH, JHS. Acquisition of data: PEP, CEK, SEA, TY, KMH, JHS. Analysis and interpretation of data: SIG, PEP, JHB, JHS. Drafting of manuscript: SIG, JHS. Critical revision of manuscript for important intellectual content: All authors. Statistical analysis: PEP, JHB.

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Significance

Obstructive sleep apnea (OSA) is associated with increased risk of cardiovascular disease and all-cause mortality; however, the mechanisms of increased risk and the associations of OSA with arterial disease are not well understood. This is the first large, longitudinal cohort study to show that sleep apnea is an independent predictor of carotid arterial injury and atherosclerosis more than 13 years later. Our findings suggest a physiological connection between OSA and carotid atherosclerosis and underscore the importance of early diagnosis and treatment of OSA to reduce future cardiovascular disease risk.

Table 1

Participant Characteristics (N=790)

Characteristic	Baseline Visit	Carotid Ultrasound Visit	AUC[1]/Weighted Mean[2]/Years Taking[3]
Age – years	47.6 (7.7)	61.1 (7.7)	-
Male sex – N (%)	440 (56)	-	-
White race – N (%)	768 (97)	-	-
Apnea-hypopnea Index – no. of events/hour*	1.2 (0.1–4.2)	2.9 (1.1–7.4)	8.8 (4.0–15.5)[1]
<5 – N (%)	611 (77)	430 (54)	-
5–15 – N (%)	115 (15)	211 (27)	-
15–30 – N (%)	40 (5)	41 (5)	-
≥30 – N (%)	16 (2)	16 (2)	-
CPAP user - N (%)	7 (1)	92 (12)	-
Body-mass index – kg/m^2	29.6 (6.0)	31.2 (7.1)	30.3 (6.1)[2]
Systolic blood pressure – mmHg	124 (14)	125 (14)	124 (12)[2]
Diastolic blood pressure – mmHg	81 (10)	77 (10)	80 (8)[2]
HDL cholesterol – mg/dL	-	-	49 (13)[2]
Glucose – mg/dL	-	-	100 (20)[2]
Smoking			-
Current Smoker – N (%)	126 (16)	73 (9)	-
Pack-years (whole sample)	59 (105)	71 (124)	71 (124)
Anti-hypertensive medication use – N (%)	103 (13)	370 (47)	3.8 (5)[3]
Lipid-lowering medication use – N (%)	35 (4)	312 (40)	2.5 (4)[3]
Anti-diabetic medication use – N (%)	12 (2)	93 (12)	0.8 (3)[3]
Mean common carotid artery IMT – mm	-	0.755 (0.161)	-
Carotid plaque presence – N (%)	-	498 (63)	-
Carotid plaque score*	-	1.0 (0.0–3.0)	-

All values are mean (standard deviation)

AUC = area under curve; CPAP = continuous positive airway pressure; HDL = high-density lipoprotein; IMT = intima-media thickness

*AHI and plaque score are reported as medians with inter-quartile ranges

Table 2

Associations of Baseline AHI and AUC-AHI with Carotid Intima-Media Thickness, Carotid Plaque Presence and Carotid Plaque Score

Predictor	IMT β*, (95% CI)	p	Plaque Presence OR, (95% CI)	p	Plaque Score OR, (95% C)	p
Baseline AHI†	0.027 (0.000, 0.054)	0.049	1.550 (1.020, 2.350)	0.041	1.300 (1.050, 1.610)	0.018
AUC-AHI‡	0.0004 (−0.0012, 0.0021)	0.608	1.037 (1.008, 1.066)	0.012	1.013 (1.001, 1.026)	0.039

AHI = apnea-hypopnea index; AUC = area under curve; CI = confidence interval; IMT = intima-media thickness

*mm per unit AHI or AUC-AHI

†Adjusted for age, sex, body-mass index, systolic blood pressure, current smoking, and use of anti-hypertensive-, anti-diabetic- and lipid-lowering medications

‡Adjusted for age, sex, weighted body-mass index and systolic blood pressure, pack-years of smoking, years of taking anti-hypertensive-, anti-diabetic- and lipid-lowering medications and weighted mean high-density lipoprotein cholesterol and glucose