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The Relationship Between Obstructive Sleep Apnea and Self-Reported Stroke or Coronary Heart Disease in Overweight and Obese Adults with Type 2 Diabetes Mellitus

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Study Objectives: Type 2 diabetes mellitus (T2DM) and obstructive sleep apnea (OSA) are common, increasingly recognized as comorbid conditions, and individually implicated in the development of cardiovascular disease (CVD). We sought to determine the association between OSA and CVD in an overweight and obese population with T2DM.

Design: Cross-sectional.

Setting: Ancillary study to the Look AHEAD trial.

Participants: Three hundred five participants of the Sleep AHEAD study who underwent unattended full polysomnography at home with measurement of the apnea-hypopnea index (AHI).

Measurements and Results: Self-reported prevalent CVD was obtained at the initial assessment of the parent study and included a history of the following conditions: stroke, carotid endarterectomy, myocardial infarction, coronary artery bypass grafting, and percutaneous coronary intervention. Logistic regression was used to assess the association of OSA, measured continuously and categorically, with prevalent CVD. OSA was present (AHI ≥ 5) in 86% of the population, whereas the prevalence of all forms of CVD was just 14%. The AHI was associated with stroke with an adjusted odds ratio (95% confidence interval) of 2.57 (1.03, 6.42). Neither the continuously measured AHI nor the categories of OSA severity were significantly associated with the other forms of CVD assessed.

Conclusions: We found suggestive evidence of a greater prevalence of stroke at greater values of the AHI. OSA was not associated with prevalent coronary heart disease in the Sleep AHEAD trial. Future studies should confirm the link between OSA and stroke and examine mechanisms that link OSA to stroke in adults with T2DM.

Keywords: Obstructive sleep apnea, stroke, cardiovascular disease, coronary heart disease, diabetes mellitus

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse during sleep, with resultant arterial hypoxemia and sleep fragmentation. It is closely associated with obesity, and excess weight has been implicated in its development.[1,2] Like OSA, type 2 diabetes mellitus (T2DM) is closely associated with obesity. The parallel rise of the obesity and T2DM epidemics dubbed "diabesity" presents a notable and increasing threat to the health of our global population.[3]

Although the common link to obesity is generally acknowledged, the relationship between OSA and T2DM is likely complex and only beginning to be understood.[4,5] Conceivably, OSA may amplify the association between obesity, insulin resistance, and ultimately T2DM via sleep fragmentation and intermittent hypoxemia. On the other hand, T2DM and OSA may be pathophysiologically independent conditions with prevalent comorbidity due to joint association with obesity or visceral adiposity.[4,6,7] In the same sample population of this report, we have previously demonstrated a high prevalence of moderate and severe OSA in obese adults with T2DM,[8] findings that have reinforced previous prevalence studies in individuals with diabetes.[9,10]

Like the common association with obesity, both OSA and T2DM have been independently implicated in contributing to greater cardiovascular morbidity and mortality. Epidemiologic studies have confirmed that severe OSA is independently associated with increased risk of cardiovascular disease (CVD) and cerebrovascular disease, as well as greater all-cause mortality.[11-14] Diabetes mellitus may be a relative coronary artery disease risk equivalent.[15] Individuals with diabetes and those with the closely associated metabolic syndrome have excess morbidity and mortality related to coronary heart disease (CHD) and stroke[16,17] that is similar to the risk associated with established CVD. Although the association of T2DM with greater CVD is known, the effect of OSA in obese individuals with diabetes remains unknown.

The objective of this current study was to examine the extent to which OSA is associated with prevalent CVD in a cohort with T2DM. We hypothesized that severe OSA would be significantly associated with prevalent CVD.

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METHODS

Participants

The Sleep Action for Health in Diabetes (AHEAD) study is an ancillary study to the Look AHEAD trial, which is a randomized controlled trial investigating the long-term effect of a lifestyle intervention in 5,145 overweight and obese individuals with diabetes mellitus. Participants in the Look AHEAD trial were overweight and obese adults with T2DM who were not actively losing weight and were able to safely complete a 2-wk run-in of dietary restriction and exercise. The details of the Look AHEAD trial and Sleep AHEAD study methods have been previously published.[8,18,19]

All participants from 4 of the 16 Look AHEAD sites were eligible for inclusion in the Sleep AHEAD study, unless they were currently treated for OSA. The initial protocol attempted to recruit Look AHEAD trial participants with high risk for OSA using a screening questionnaire. This criterion was dropped when nearly all of the 1st 80 participants screened had OSA at the time of polysomnography. A total of 306 participants were enrolled in the Sleep AHEAD study. One participant with central sleep apnea was removed from these analyses to focus on OSA, leaving 305 participants. The 305 Sleep AHEAD study participants were representative of Look AHEAD trial participants at the 4 clinical sites except for older age (61.3 ± 6.5 versus 58.7 ± 6.9 yr; $P < 0.0001$) and lower hemoglobin A1c values (7.2 ± 1.1 versus 7.4 ± 1.2%; $P = 0.03$).[8] The Institutional Review Board at each site approved the Sleep AHEAD study protocol and each participant signed written informed consent.

Sleep Measures

Daytime sleepiness was assessed using the Epworth Sleepiness Scale.[20] A single night, home unattended overnight polysomnogram (PSG) was obtained (Compumedics PS2, Abbotsville, Australia). The techniques and protocol developed for the Sleep Heart Health Study (SHHS) were used and standard scoring was done at a central reading center (University of Pennsylvania). The channels recorded included electroencephalograms (C_3M_2, C_4M_1), bilateral electrooculograms, chin muscle activity, rib cage and abdominal movement (piezoelectric crystal), nasal pressure via cannula, oronasal thermistor, snoring from the nasal pressure signal, body position, electrocardiogram, and oxygen saturation.

The PSGs were scored according to the criteria established by the American Academy of Sleep Medicine.[21] The primary measurement of the PSG was the apnea-hypopnea index (AHI), quantified as the total number of apneas and hypopneas per hr of sleep. Apneas were defined as a 90% or greater decrease in airflow from baseline for at least 10 sec. They were further classified as obstructive or central based on the presence or absence, respectively, of respiratory-related chest wall movement. Hypopneas were defined as a 30% to 90% reduction in airflow from baseline lasting 10 sec in conjunction with a ≥ 4% desaturation. The oxygen desaturation index (ODI) was calculated by dividing the total number of ≥ 4% oxygen desaturation events by hr of sleep time.

Anthropometric Measures

Standard methods were used to measure height, weight, and waist and neck circumferences.[19,22] The body mass index (BMI) was calculated as the weight in kilograms divided by the squared height in meters.

Cardiovascular Disease

The term total CVD is used to broadly encompass both CHD and cerebrovascular disease. Prevalent prior stroke, carotid endarterectomy, myocardial infarction, coronary artery bypass grafting, and percutaneous coronary intervention were defined by patient self-report during structured interviews at the time of the baseline assessment in the Look AHEAD trial. Cerebrovascular disease included stroke and carotid endarterectomy, whereas CHD included total myocardial infarction, coronary artery bypass grafting, and percutaneous coronary intervention.

Statistical Analysis

Characteristics of the participants were summarized as proportions or means (standard deviation, SD). Baseline covariates were stratified by sex due to anthropometric differences. To provide a clinical interpretation and to examine for a nonlinear threshold effect, the AHI severity was categorized for analysis. Because of the high prevalence of moderate and severe OSA, categories of the AHI were created with clinical cutoffs of < 15, 15 to < 30, and ≥ 30 (representing no or mild, moderate, and severe OSA, respectively). Because less than 14% of this cohort had an AHI < 5 (n = 41), we elected to group no OSA (AHI < 5) with mild OSA (AHI 5-14) for analysis. Across these strata, CVD risk factors as well as prevalence were examined.

The association of OSA with prevalent CVD was determined with logistic regression. Due to nonnormality in the right-skewed distribution of the AHI, the sum of the AHI+1 was log-transformed and used as an independent variable for multiple logistic regression models with the CVD parameters as dependent variables. Unadjusted and adjusted multivariable models were developed. Models were adjusted for age, sex, race, BMI, and hemoglobin A1c. Hemoglobin A1c was included in the adjusted models to account for the fact that all individuals in this cohort have T2DM with variable levels of glucose control.

The AHI was used as a categorical independent variable for logistic regression. Clinical categories of OSA severity were defined for no OSA or mild OSA, moderate OSA, and severe OSA. Models were similarly adjusted to those using the continuous AHI measure. The data analysis for this article was performed in Proc Mixed software (SAS, version 9; SAS Institute Inc, Cary, North Carolina).

RESULTS

The baseline demographics and sleep parameters relevant to this analysis are summarized in Table 1. The mean (SD) age was 61.5 ± 6.5 yr and BMI was 36.5 ± 6.5 kg/m^2. Although there was no difference in BMI between men and women, men had greater values for weight, height, neck and waist circumference (all $P < 0.0001$), and hemoglobin A1c ($P = 0.03$).

OSA (AHI ≥ 5) was present in 86% of the cohort. The mean (SD) AHI was 20.5 (16.8) and ODI was 17.6 (14.7) events/hr. The AHI ($P = 0.001$) and ODI ($P = 0.03$) were greater in men than women. The degree of daytime sleepiness was not different between men and women based on the Epworth Sleepiness Scale.

The prevalence of individual types of CVD at baseline was low, < 10%. Table 2 shows the distribution of OSA severity cat-

Table 1—Sleep AHEAD study participant baseline characteristics

	Overall	Men	Women
Number of participants	305	122	183
Race/ethnicity, %			
White	73.0	90.1	61.8
African American	19.1	6.6	27.3
Other	7.9	3.3	10.9
Age, yr	61.5 ± 6.5	61.4 ± 7.1	61.3 ± 6.1
Body mass index, kg/m^2	36.5 ± 5.8	36.1 ± 5.6	36.7 ± 5.9
Weight, kg	101.7 ± 18.0	110.7 ± 16.5	95.6 ± 16.2
Height, cm	167.0 ± 9.7	175.5 ± 7.0	161.3 ± 6.6
Waist circumference, cm	115.0 ± 13.0	120.9 ± 12.1	111.0 ± 12.1
Neck circumference, cm	41.4	44.4 ± 3.2	39.0 ± 3.1
Hemoglobin A1c, %	7.2	7.4 ± 1.1	7.1 ± 1.0
Hypertension, %	87.2	88.5	86.3
Current smoker, %	5.9	6.6	5.5
Past smoker, %	47.2	53.7	42.9
Apnea-hypopnea index,[a] events/hr	20.5 ± 16.8	24.6 ± 18.6	17.8 ± 15.0
Oxygen desaturation index,[b] events/hr	17.6 ± 14.7	20.0 ± 15.9	15.9 ± 13.7
Participants with > 10% of time below 90% saturations, %	16.1	20.5	13.1
Epworth Sleepiness Scale score	7.9 ± 4.6	8.0 ± 4.5	7.8 ± 4.7

[a]Hypopneas required ≥ 4% desaturation. [b]Index of ≥ 4% desaturations.

Table 2—Prevalence of cardiovascular disease and cardiovascular disease risk factors by OSA severity

	OSA Severity Category			
	AHI < 15 (No or Mild)	AHI 15 – 29 (Moderate)	AHI ≥ 30 (Severe)	P value
Number of participants	143	93	69	
Cardiovascular disease				
Cerebrovascular disease, %	2.1	7.5	5.8	0.16
Stroke	1.4	5.4	5.8	0.06
CEA	0.7	2.2	0	0.63
Coronary heart disease, %	10.5	15.1	15.9	0.44
Myocardial infarction	7.0	10.8	11.6	0.46
CABG	2.8	6.5	5.8	0.35
PCI	6.3	6.5	11.6	0.71
Cardiovascular disease risk factors				
Hypertensive, %	83.2	89.3	92.8	0.12
Systolic blood pressure, mm Hg	130 ± 18	130 ± 18	132 ± 18	0.72
Diastolic blood pressure, mm Hg	69 ± 9	69 ± 8	71 ± 10	0.33
Body mass index, kg/m^2	35.5 ± 5.4	35.7 ± 5.3	39.0 ± 5.8	< 0.001
Smoking status				0.17
Current, %	7.0	7.5	1.5	
Former, %	43.7	44.1	58.8	
Never, %	49.3	48.4	39.7	
Total cholesterol, mg/dL	189 ± 36	197 ± 43	193 ± 36	0.32
LDL cholesterol, mg/dL	112 ± 30	118 ± 34	114 ± 32	0.39
HDL cholesterol, mg/dL	46 ± 13	46 ± 11	43 ± 12	0.32
T-Chol:HDL ratio	4.4 ± 1.3	4.5 ± 1.3	4.8 ± 1.5	0.15
Lipid lowering medication, %	51.4	50.5	59.4	0.47
Hemoglobin A1c, %	7.2 ± 1.2	7.2 ± 1.0	7.3 ± 1.0	0.78

Categorical variables displayed as percentages, continuous variables presented as mean ± standard deviation. P values represent the results of chi-squared tests (categorical) or 1-way analysis of variance (continuous) for differences among groups. Smoking status missing 2 values. Lipid medication missing 1 value. AHI, apnea-hypopnea index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; CEA, carotid endarterectomy; LDL, low-density lipoprotein; HDL, high-density lipoprotein. T-Chol, total cholesterol.

Table 3—Logistic regression of prevalent cardiovascular disease (dependent) using continuous AHI (Log[AHI+1])

	Unadjusted		Adjusted[a]	
	OR (95% CI)	P value	OR (95% CI)	P value
Cerebrovascular disease				
Stroke	2.16 (0.96,4.84)	0.06	2.57 (1.03,6.42)	0.04
CEA	1.28 (0.37,4.48)	0.70	–	–
Coronary heart disease				
MI	1.16 (0.77,1.73)	0.48	0.94 (0.61,1.47)	0.80
CABG	1.35 (0.74,2.48)	0.33	1.24 (0.65,2.37)	0.51
PCI	1.27 (0.80,2.01)	0.32	1.01 (0.62,1.67)	0.96
Total cardiovascular disease[b]	1.26 (0.91,1.76)	0.17	1.11 (0.77,1.59)	0.59

[a]Model adjusted for age, sex, race, body mass index, and hemoglobin A1C. [b]Includes MI, CABG, PCI, stroke, and CEA. Adjusted model for CEA did not converge. CABG, coronary artery bypass grafting; CEA, carotid endarterectomy; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 4—Logistic regression of cardiovascular disease using obstructive sleep apnea severity category.

	OSA severity category		
	AHI < 15 OR (Referent)	AHI 15 – 29 OR (95% CI), P value	AHI ≥ 30 OR (95% CI), P value
Cerebrovascular disease			
Univariate model	1.0	3.22 (0.79,13.2), 0.10	2.87 (0.63,13.2), 0.18
Adjusted model[a]	1.0	3.50 (0.84,14.7), 0.09	3.25 (0.63,13.8), 0.16
Coronary heart disease			
Univariate model	1.0	1.51 (0.62,3.30), 0.30	1.62 (0.70,3.74), 0.26
Adjusted model[a]	1.0	1.56 (0.65,3.77), 0.32	0.97 (0.36,2.60), 0.95
Total cardiovascular disease[b]			
Univariate model	1.0	1.78 (0.86,3.66), 0.12	1.72 (0.78,3.78), 0.18
Adjusted model[a]	1.0	1.81 (0.83,3.97), 0.14	1.19 (0.48,2.94), 0.70

[a]Model adjusted for age, sex, race, body mass index, and hemoglobin A1C. [b]Includes myocardial infarction (MI), coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), stroke, and carotid endarterectomy (CEA). Individual types of cardiovascular disease (MI, CABG, PCI, stroke, and CEA) were not tested due to small case numbers across the 3 categories of obstructive sleep apnea severity. AHI, apnea-hypopnea index; CI, confidence interval; OR, odds ratio.

egories in the study population and the prevalence of CVD and CVD risk factors across OSA severity. CHD and stroke were more prevalent with increasing severity of OSA, although this finding was not statistically significant. The BMI of those with severe OSA was 39.0 ± 5.8 kg/m^2, compared with 35.5 ± 5.4 and 35.7 ± 5.3 in those with no or mild OSA and those with moderate OSA, respectively ($P < 0.001$). Otherwise, there were no significant differences across OSA groups in the prevalence of hypertension HTN, smoking status, or other important risk factors for CVD (Table 2).

Table 3 shows the results of unadjusted and adjusted models using logistic regression to model the association between the dependent CVD measures and the independent continuous measure of OSA severity. With the exception of stroke, the AHI was not associated with greater likelihood of prevalent CVD in adjusted analyses. The adjusted odds ratio (OR) for stroke was 2.57 (1.03, 6.42).

Table 4 displays the association of OSA severity by clinical category with the various forms of prevalent CVD. Although the adjusted OR for prevalent cerebrovascular disease in those with moderate OSA, 3.50 (0.84, 14.7), and severe OSA, 3.25 (0.63, 13.8), were elevated compared with those with no or mild OSA, these results were not statistically significant. The presence of moderate or severe OSA was not associated with greater likelihood of prevalent CVD compared with those with no or mild OSA.

DISCUSSION

In this baseline analysis of the Sleep AHEAD study, greater AHI values were associated with greater prevalence of stroke with a fully adjusted OR of 2.57 (1.03, 6.42). Although many of the relationships between the AHI or clinical severity of OSA appear to show greater likelihood of prevalent CVD, these findings were not statistically significant.

Our finding of greater stroke at increasing levels of the AHI could suggest that OSA may further augment the already substantial CVD morbidity and mortality risk in overweight and obese adults with T2DM. The cerebral circulation is increasingly recognized as an important vascular bed with regard to the vascular implications of OSA. This cross-sectional analysis of adults with T2DM may line up with long-term follow up of incident stroke in community-based adult populations in

both the Wisconsin Sleep Cohort[14] and the recently published findings from the SHHS.[13] These longitudinal studies appear to show an approximately 3-fold greater risk of incident stroke in those with severe OSA compared with those without OSA, but are poorly defined with respect to T2DM. The excess risk for incident stroke is attenuated to statistical nonsignificance with full covariate adjustment in the smaller Wisconsin Sleep Cohort (OR 3.08 [0.74, 12.81], P = 0.12). In the SHHS, however, the statistically significant finding was limited to men but persisted after full covariate adjustment (OR 2.86 [1.10, 7.39]).

The lack of a stronger association with CHD is also in line with the latest epidemiologic data. The 10-year follow-up of the SHHS shows only an equivocal association between OSA and incident CHD, which is limited to middle-aged men.[23] The OR for incident CHD in all men was 1.45 (0.99, 2.13) after adjustment for age, race, BMI, and smoking. Our study seems to show that an association of OSA with cerebrovascular disease may exist, whereas there is no association with excess CHD in this limited sample of obese adults with T2DM.

The findings detailed in this article must be interpreted in the context of our limitations. First, the limited sample of adults with T2DM is not amenable to a fully powered analysis of CVD association to OSA due to the limited number of cases of CVD but a high prevalence of OSA. The low prevalence of CVD in this obese population of adults with T2DM is surprising, but likely reflects the fact that participants in the parent Look AHEAD trial were required to pass a cardiac treadmill test for safe inclusion in the intensive lifestyle intervention being tested. When coupled with the high prevalence of OSA, our limited sample of CVD cases reduces the power of this cross-sectional analysis. The Sleep AHEAD study was powered for its primary objective[18] to determine the effect of weight loss on sleep apnea. Second, self-report of prevalent CVD could lead to some misclassification bias that could further decrease power, but this should be random with respect to the presence of OSA. Further, given the night-to-night variability in OSA and our single night of PSG data, some misclassification bias could also be present with respect to OSA severity. Due to small numbers without OSA and unclear consequences of mild OSA with respect to cardiovascular morbidity and mortality,[24] we chose to combine the groups with no or mild OSA. This could further bias our results to the null by having some participants in the referent group that suffered from mild OSA. The cross-sectional design of this study precludes any inference of causality.

CONCLUSION

We found evidence for greater likelihood of prevalent stroke at greater values of the AHI, suggesting the presence of moderate and severe OSA may further increase stroke risk in obese adults with T2DM. OSA was not associated with baseline CHD in the Sleep AHEAD study. Future studies should confirm the association of stroke and OSA, examine mechanisms that link OSA to stroke, and determine the direction of causality in adults with T2DM.

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This was not an industry supported study. Dr. Sanders is a scientific consultant to Philips-Respironics and is a coinventor of BiPAP® brand and related technologies patents which have been assigned to Philips-Respironics for use with their BiPAP® brand and related technologies and in exchange for a royalty interest. He is an Editor-in-Chief and a Section Editor (Sleep Medicine Section) for UpToDate for which he receives compensation. He is a Field Editor for *SLEEP MEDICINE* for which he receives compensation. He is a Deputy Editor for *SLEEP*. Dr. Kuna received grant support from Philips-Respironics. Dr. Zammit has received grants and or research support from Abbott, Actelion, Ancile, Apnex, Arena, Aventis, Cephalon Inc., CHDI, Elan, Epic, Evotec, Forest, Galderma, Glaxo Smith Kline, H. Lundbeck A/S, King, Merck and Co., National Institute of Health (NIH), Neurim, Neurocrine Biosciences, Neurogen, Organon, Orphan Medical, Otsuka, Pfizer, Predix, Respironics, Sanofi-Aventis, Sanofi-Synthelabo, Schering-Plough, Sepracor, Shire, Somaxon, Takeda Pharmaceuticals North America, Targacept, Thymon, Transcept, UCB Pharma, Ultragenyx, Predix, Vanda, Wyeth-Ayerst Research, 2) Consultant for Actelion, Alexza, Arena, Aventis, Biovail, Boehringer-Ingelheim, Cephalon, Elan, Eli Lilly, Evotec, Forest, Glaxo Smith Kline, Jazz, King Pharmaceuticals, Ligand, McNeil, Merck, Neurocrine Biosciences, Organon, Pfizer, Renovis, Sanofic-Aventis, Select Comfort Sepracor, Shire, Somnus, Takeda Pharmaceuticals, Vela, Wyeth, 3) Honoraria from Neurocrine Biosciences, King Pharmaceuticals, McNeil, Sanofi-Aventis, Sanofi-Synthelabo, Sepracor, Takeda Pharma-

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