Combined Effects of Sleep Disordered Breathing and Metabolic Syndrome on Endothelial Function: The Wisconsin Sleep Cohort Study

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Study Objectives: To examine the combined impact of sleep disordered breathing (SDB) and metabolic syndrome (MetS) in endothelial dysfunction.
Design: Cross-sectional assessment of endothelial function, MetS and SDB status in a population-based sample.
Setting: Community-based cohort.
Participants: Participants (n = 431) from the Wisconsin Sleep Cohort were studied between 2004 and 2007. MetS was defined following the National Cholesterol Education Program criteria. SDB severity was defined by the apnea-hypopnea index ([AHI] events/h of sleep) during overnight polysomnography. Fasting lipids, glucose, and insulin were measured and homeostasis model assessment was calculated to quantify insulin resistance (HOMA-IR). Multivariable linear regression was used to assess associations of brachial artery flow-mediated dilation (FMD) with SDB, MetS, and their interaction.
Intervention: None.
Measurements and Results: Participants averaged 60.2 years of age (SD 7.8 years), 44% were female, and 97% Caucasian. MetS was present in 35%; 22% had AHI ≥ 15 events/hour. Of the no-MetS group, 7% had AHI ≥ 15 events/hour. FMD (mean 5.5%; SD 3.5%) was inversely associated with age (r = -0.16, P = 0.001) and mean brachial artery diameter (r = -0.29, P < 0.001). Multivariate linear models adjusted for CVD risk factors showed that the negative association between SDB and FMD was present among subjects with MetS (β $FMD_{per\ unit\ log2(AHI+1)}$ = -0.55%, P = 0.014), but not among subjects with normal metabolic function (β = 0.13, not significant), P for interaction = 0.011.
Conclusion: Sleep disordered breathing and concurrent metabolic syndrome are synergistically associated with worse endothelial function. Individuals with both of these conditions appear to be at a significantly higher risk for cardiovascular disease complications.
Keywords: endothelial function, cardiovascular disease, metabolic syndrome, sleep apnea, obesity
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INTRODUCTION

Sleep disordered breathing (SDB) is characterized by repetitive episodes of partial or total airway obstruction leading to intermittent hypoxia, repetitive arousals, sleep fragmentation, and sympathetic activation. SDB has been associated with increased risk of hypertension, coronary artery disease, atrial fibrillation, stroke, and cardiovascular disease (CVD) mortality.[1-4] Large epidemiological studies have shown that SDB is highly prevalent; up to one-third of middle-aged adults have mild or worse SDB (apnea-hypopnea index [AHI] ≥ 5 events/h of sleep); 13% have AHI ≥ 15 events/hour.[5,6]

Metabolic syndrome (MetS) is defined as a cluster of cardiovascular and metabolic abnormalities including central obesity, insulin resistance, dyslipidemia, and hypertension. The prevalence of MetS is estimated to be approximately 34% of the adult US population.[7] Its prevalence is significantly higher in overweight and obese older adults, and it is associated with increased CVD risk and the development of type 2 diabetes mellitus.

Endothelial dysfunction has been linked with SDB and its sequelae, including HTN and metabolic derangements.[1,8-10] Mechanistically, SDB is thought to promote a pro-inflammatory state with increased oxidative stress and lower nitric oxide availability, ultimately leading to endothelial dysfunction.[11-14] It remains unclear whether SDB or obesity independently alters endothelial function.[15] Use of continuous positive airway pressure (CPAP) has been shown to mitigate the deleterious effects of SDB on endothelial function regardless of body mass index (BMI) or waist circumference.[16,17] The concomitant presence of metabolic syndrome in subjects with SDB is very common due to shared anatomic and functional[18] risk factors and their possible independent association.[2,]The relationship between sleep apnea and insulin resistance in obese patients has been described as a "bi-directional, feed forward, pernicious model."[19] We previously demonstrated an increased odds for MetS with increased SDB severity, independent of obesity, in the Wisconsin Sleep Cohort.[20]

In this study we used brachial artery flow-mediated dilation (FMD) as a marker of endothelial function and CVD risk in subjects with SDB. Our objective was to determine if there was an interaction of MetS and SDB in their association with endothelial dysfunction such that the presence of both MetS and SDB predicted a greater-than-additive impact on endothelial dysfunction, independent from obesity and other CVD risk factors.

METHODS

Participants

This study was approved by the University of Wisconsin Health Sciences Institutional Review Board. All participants provided written informed consent. The Wisconsin Sleep

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Cohort Study is an ongoing longitudinal, community-based study of SDB recruited from 5 State of Wisconsin agencies.[5] The present analysis includes a subset of this cohort (n = 431) who underwent complete in-hospital polysomnograms (PSG); brachial artery reactivity testing with FMD measurement; morphometric assessment including neck, waist, hip circumference, height, and weight; brachial blood pressures; fasting lipid panels; and glucose and insulin levels. As an ancillary study to the Wisconsin Sleep Cohort Study, there was no special selection of this sample. All Wisconsin Sleep Cohort participants scheduled for sleep studies over the funded study period were included in this sub-study as long as they consented to the FMD procedure and were not medically excluded. Participants who used CPAP during PSG or at home were not included in these analyses.

FMD measurements were collected initially at daytime visits conducted between October 14, 2004, and December 4, 2007. The average interval for the 431 participants between PSG and morphometric assessment, serum collection and FMD testing was 1.6 (0.6) years (range 0.6-3.0 years).

Polysomnography

Results from the PSG performed closest to the MetS assessment and endothelial function testing were used for the present analyses. Sleep studies were performed at the Clinical Research Unit of the University of Wisconsin Hospitals and Clinics. A PSG system (Grass Instruments, Quincy, MA) was used to assess sleep state and respiratory and cardiac parameters. Sleep state was determined by electroencephalography, electrooculography, and electromyography. Arterial oxyhemoglobin saturation, oral and nasal airflow, nasal air pressure, and thoracic cage and abdominal respiratory motion were used to detect SDB events. Oxyhemoglobin saturation was recorded by pulse oximetry (Ohmeda 3740, Englewood, CO). Thermocouples (ProTec, Hendersonville, TN) were used to detect airflow. A pressure transducer (Validyne Engineering Corp., Northridge, CA) measured air pressure at the nares. Respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY) was used to record thoracic and abdominal excursions. Sleep state and respiratory event scoring was performed by trained sleep technicians. Each 30-sec epoch of the polysomnographic records was scored for sleep stage using conventional criteria (Rechtschaffen & Kales) [21] and for breathing events. Cessation of airflow lasting ≥ 10 sec defined an apnea event. A discernible reduction in the sum of thoracic plus abdomen respiratory inductance plethysmography amplitude associated with ≥ 4% reduction in oxyhemoglobin saturation defined a hypopnea event. The average number of apnea plus hypopnea events/h of sleep defined the apnea-hypopnea index (AHI), a summary parameter of SDB. AHI severity was divided into the following groups (0–4.9, 5–14.9, and ≥ 15 events/h or any CPAP use) when analyzed as a categorical variable.

Metabolic Syndrome

MetS was defined using the 2004 updated National Cholesterol Education Program criterion by NHLBI/AHA in accordance with the American Diabetes Association (≥ 3 of the following criteria: waist circumference > 40 inches (102 cm) in men or > 35 inches (88 cm) in women; blood pressure ≥ 130/85 mm Hg or taking blood pressure-lowering medication; triglycerides ≥ 150 mg/dL; high-density lipoprotein cholesterol < 40 mg/dL in men or < 50 mg/dL in women; and fasting glucose > 100 mg/dL).[22,23]

For our analysis, a participant who self-reported being diagnosed by a physician with type 2 diabetes mellitus or who reported taking a diabetes medication were classified as having MetS. Type 1 diabetic individuals were excluded from this analysis. Weight, height, blood pressure, waist, hip, and neck girth were measured by research technicians. Fasting blood samples and urine samples were collected by trained nursing staff. The homeostasis model assessment method to characterize insulin resistance (HOMA-IR) was calculated using fasting insulin and glucose values as: HOMA-IR = insulin (μU/mL) * glucose (mmol/L) / 22.5.[24]

Information on CPAP use, medication use, alcohol consumption (number of drinks/week), current smoking status, race, and CVD events (heart attack, stroke, angina, congestive heart failure, coronary bypass surgery, coronary or balloon angioplasty, pacemaker insertion, coronary artery stent) were collected by self-report.

Ultrasound Measurement of Flow-Mediated Dilation

Endothelial function was evaluated by measuring brachial artery FMD with high-frequency ultrasound. A detailed protocol has been published previously.[25] Briefly, all FMD scans were performed after 10 hours of fasting, in the morning, in a temperature-controlled room in a supine position after 10 minutes of rest. Imaging was performed with an 8-MHz linear array transducer in an Acuson Sequoia C512 ultrasound system (Siemens Medical Solutions, Issaquah, WA) by a trained sonographer. The brachial artery was located above the elbow and scanned longitudinally. Extravascular landmarks were identified and labeled to assure reproducibility after cuff release.

After recording baseline B-mode images of the brachial artery and spectral Doppler velocities, the forearm cuff was inflated to 250 mm Hg for 5 min to induce reactive hyperemia. Immediately after deflation, spectral Doppler velocities were re-obtained to verify hyperemia. Brachial artery B-mode images were obtained at 60 and 90 sec after cuff release, recording 3-5 cardiac cycles at each time point. Studies were stored digitally; brachial artery end-diastolic diameters were measured in triplicate by a single reader blinded to participant information using a Vericis reading station (Camtronics Medical Systems, Inc, Hartland, WI). FMD was measured for all participants at 2 time points, 60 and 90 sec after cuff release, and calculated as the change in brachial artery diameter relative to the resting brachial artery diameter expressed as a percentage (FMD, %). The outcome variable used in our models was the highest FMD for a given participant; obtained at either 60 or 90 sec post cuff release. Mean brachial artery diameter (included as a covariate in the models predicting FMD) was defined as the average between the resting diameter and the maximum diameter observed post cuff deflation.[26] In our laboratory, subjects who underwent repeat FMD scans approximately 2 weeks apart had an inter-scan ΔFMD% of only 0.26% (-0.43% to +0.72%, P = 0.498); the median inter-reader variability was -0.14% to +0.09%, with correlations of 0.97-0.99 (P < 0.001).[27]

Table 1—Baseline characteristics by metabolic syndrome status.

Part I

	Metabolic Syndrome (N = 152)					No Metabolic Syndrome (N = 279)					
Baseline Characteristic	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**P-value**
Age (years)	61.0	8.2	61.3	54.6	67.8	59.7	7.6	59.2	53.9	65.2	0.091
Body mass index (kg/m^2)	34.8	6.3	34.1	30.3	38.2	27.8	5.0	27.0	24.6	29.9	< 0.001
Waist circumference (cm)	109.1	12.7	108.4	101.0	117.6	91.7	11.6	91.5	84.5	98.8	< 0.001
AHI (events/h)	10.2	9.9	7.8	2.9	13.1	5.5	7.2	3.0	0.8	7.5	< 0.001
$\log_2$(AHI+1) (events/h)	3.0	1.3	3.1	2.0	3.8	2.0	1.4	2.0	0.8	3.1	< 0.001
Mean SO_2 sleep (%)	94.3	2.4	94.6	93.5	95.7	95.5	1.7	95.7	94.6	96.7	< 0.001
Years between PSG and FMD	1.6	0.6	1.6	1.0	2.0	1.6	0.6	1.5	1.1	2.1	0.522
Resting brachial diameter (mm)	4.7	0.8	4.7	4.1	5.2	4.4	0.8	4.4	3.9	5.0	0.007
Mean brachial diameter (mm)	4.8	0.7	4.9	4.2	5.3	4.6	0.8	4.5	4.0	5.1	0.010
FMD (%)	5.1	3.6	4.3	2.7	7.4	5.8	3.4	5.5	3.4	7.8	0.028
Systolic blood pressure (mm Hg)	128.4	14.4	127.0	119.0	137.5	119.1	12.2	119.0	110.0	127.3	< 0.001
Diastolic blood pressure (mm Hg)	79.1	9.9	80.0	71.0	86.0	76.7	8.5	77.0	70.0	82.0	0.021
Glucose (mg/dL)	116.9	26.5	110.0	103.0	124.0	96.6	11.1	95.0	90.0	101.0	< 0.001
Insulin (μU/mL)	18.2	14.7	16.0	10.0	21.0	9.0	5.7	8.0	5.0	11.0	< 0.001
HOMA-IR	4.8	3.7	3.9	2.5	5.4	2.2	1.6	1.8	1.2	2.7	< 0.001
Triglycerides (mg/dL)	160.6	73.6	157.0	102.0	205.0	98.2	50.8	88.0	57.0	128.0	< 0.001
HDL (mg/dL)	52.6	13.7	51.0	43.0	58.0	62.8	15.4	61.0	51.0	72.0	< 0.001
Alcoholic consumption (drinks/week)	3.9	5.7	2.0	0.0	6.0	4.0	4.7	3.0	0.0	6.0	0.230

Part II

	Metabolic Syndrome		No Metabolic Syndrome		
	N	**%**	**N**	**%**	**P-value**
Sex (female)	75	49.0	113	40.5	0.077
Cholesterol medication use	73	48.0	81	29.0	< 0.001
Hypertension	108	71.1	82	29.4	< 0.001
Current smoker	11	7.2	31	11.1	0.195
Any cardiovascular event	24	15.8	18	6.5	0.002
AHI					< 0.001
0 to < 5	52	34.2	174	62.4	
5 to < 15	67	44.1	86	30.8	
15 to < 30	24	15.8	14	5.0	
≥ 30	9	5.9	5	1.8	
Number of Metabolic Syndrome Risk Factors*					< 0.001
0			67	24.0	
1			113	40.5	
2			99	35.5	
3	70	46.1			
4	32	21.1			
5	7	4.6			
Diabetes Mellitus	43	28.3			

Q1, Quartile 1 (25th percentile); Q3, Quartile 3 (75th percentile); AHI, apnea-hypopnea index; FMD, flow-mediated dilation; HOMA-IR, homeostatic model assessment–insulin resistance; HDL, high-density lipoprotein cholesterol; PSG, polysomnogram. *Diabetes mellitus subjects were automatically included in MetS group, and are listed as a separate risk factor.

Statistical Analysis

All analyses were performed with SAS software, release 9.2 (SAS Institute, Inc., Cary, NC). Spearman correlations with adjustment for age, gender, and mean brachial artery diameter were computed between FMD and the continuous variables. Wilcoxon nonparametric statistics were computed to compare FMD by the categorical variables. Descriptive results are expressed as means (standard deviations), medians (lower and upper quartiles), or total counts and proportions when appropriate. AHI was incorporated in the models as a continuous

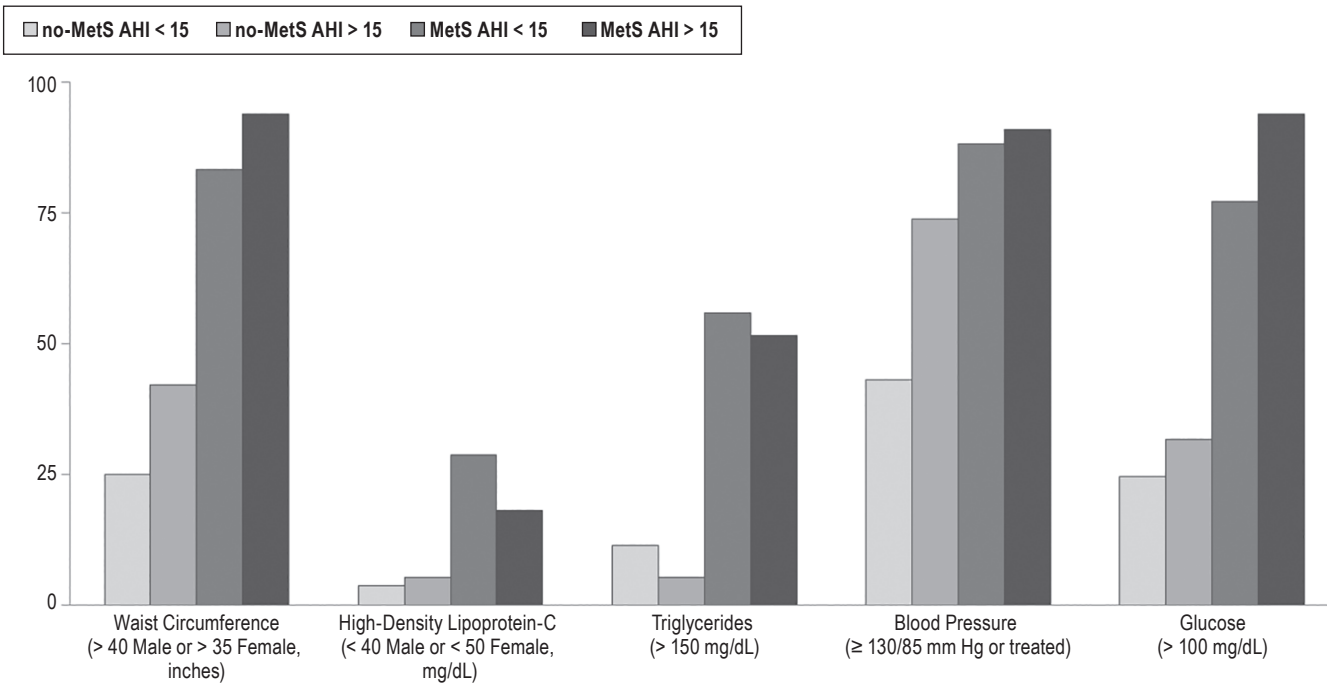

Figure 1—Percent distribution of metabolic syndrome components by SDB severity.

variable (log_2(AHI+1), "logAHI") or as an ordinal variable as defined above (n = 431). HOMA-IR was not available for 29 subjects due to missing insulin measurements. Since the use of insulin or oral diabetic medications can affect the validity of HOMA-IR as an indicator,[28] subjects who self-reported a diagnosis of diabetes mellitus or were taking diabetes medication (n = 47) were excluded from these analyses, leaving 363 subjects with complete data for the models evaluating HOMA-IR.

Multivariable linear regression models were tested to determine the influence of SDB on insulin resistance (HOMA-IR). These models included age, gender, alcohol consumption, waist circumference and its interaction with AHI as covariates.

In addition, stratified multivariable linear models were used to assess whether MetS modified the apparent effect of SDB on FMD. All models of FMD included mean brachial artery diameter as a covariate. To ascertain individual influence on FMD and on the overall MetS and SDB association, age, gender, and current smoking status were added incrementally to the FMD models; BMI was added in a final step based on their hypothesized influence on the outcome variable, brachial artery FMD. Least square mean FMDs were computed for each AHI category and MetS status based on the final model which included mean brachial artery diameter, gender, age, BMI, and current smoking status. We did not include alcohol consumption, anti-hypertension medication, statin use, and angiotensin-converting enzyme inhibitor use in these models because they were not associated to FMD in our subjects.

RESULTS

Demographic characteristics of the 431 participants are shown in Table 1. Participants averaged 60.2 years of age [SD, 7.8 years], 188 (44%) were female, and 419 (97%) were Caucasian. The mean BMI was 30.3 [6.4] kg/m^2. Those with MetS had significantly higher BMI (34.8 [6.3] vs. 27.8 [5.0] kg/m^2, $P < 0.001$) and waist circumference (109.1 [12.7] vs. 91.7 [11.6] cm, $P < 0.001$) compared to participants without MetS. Those with MetS also had on average higher AHI (10.2 [9.9] vs. 5.5 [7.2], $P < 0.001$) compared to those without it. In participants with moderate to severe AHI (≥ 15 AHI/h), those with MetS still had significantly higher BMI (37.0 [7.9] vs. 29.8 [4.5] kg/m^2, $P < 0.001$) and waist circumference (115.6 [12.5] vs. 97.0 [12.3] cm, $P < 0.001$). The distribution of MetS risk factors by SDB severity is presented in Figure 1. Participants with MetS had worse endothelial function (lower FMD) that those without MetS (5.1 [3.6]% vs. 5.8 [3.4]%, $P = 0.028$). HOMA-IR, as expected, was significantly higher in those with MetS ($P < 0.001$). In multivariable models that included age, sex, alcohol consumption, LogAHI, waist circumference, and the interaction between logAHI * waist circumference, HOMA-IR was significantly associated with sex, waist circumference, logAHI, and the interaction between logAHI * waist circumference ($\beta = 0.025$, $P < 0.0001$).

In univariate analysis, FMD was inversely correlated with age ($r = -0.13$, $P = 0.006$) and mean brachial artery diameter ($r = -0.22$, $P < 0.001$). After adjusting for age, sex, and mean brachial artery diameter, negative associations were seen with systolic blood pressure ($r = -0.11$, $P = 0.029$). Independent of MetS status, neither AHI ($r = -0.06$, $P = 0.218$) nor mean nocturnal O_2 saturation ($r = 0.09$, $P = 0.071$) were significantly correlated with FMD. Similarly, independent of SDB parameters, none of the individual MetS components as categorical variables, the total count of the possible 5 MetS components or HOMA-IR were significantly associated with FMD. Similar results were obtained when MetS (presence/absence) were included in models (not shown).

To address our main study hypothesis, we examined a logAHI * MetS interaction term, which we found statistically

significantly associated with FMD both without and with adjustment for multiple potential confounding variables (Table 2). In the fully adjusted model (Table 2, model 5), the estimated β-coefficient for the term logAHI * MetS (β = -0.64, P = 0.011) indicates a significant negative association between SDB and FMD. As shown in the stratified analyses in Table 3, in subjects with MetS, for each twofold increase in the AHI (an increase in one unit in $\log_2$[AHI]), there is an estimated reduction in FMD of 0.55% (P = 0.015) (Table 3, Model 2, MetS status = yes). We also analyzed the subjects divided into 3 AHI categories (0–4.9, 5–14.9, and ≥ 15 events/h) using the no-MetS and AHI 0–4.9 as reference adjusting for age, sex, mean brachial diameter, BMI, and current smoking status (Figure 2), and also found a statistically significant interaction between MetS and categorical AHI in this model, the test for trend for the interaction term was P = 0.003 (Table 4).

By contrast, there was no significant association between SDB and FMD in no-MetS participants (β = 0.13, P = 0.42), with only mean diameter and age as significant predictors. In supporting models that included logAHI and the separate MetS risk factors (systolic and diastolic blood pressure, glucose, high-density lipoprotein cholesterol, triglycerides, waist

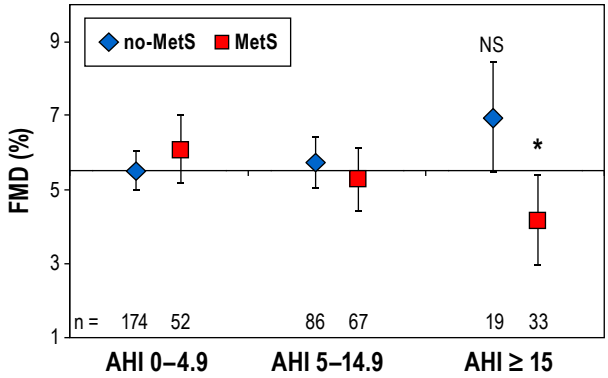

Figure 2—Flow-mediated dilation (FMD) by AHI categories and metabolic syndrome status. * P < 0.05 vs AHI 0–4.9, NS = not significant vs AHI 0–4.9 and no-MetS. FMD least square means and confidence intervals plotted for each group after adjustment for mean brachial artery, age, sex, BMI, and current smoker.

Table 2—Multivariable models of FMD as predicted by metabolic syndrome and AHI.

Model	Variables	β Estimate	SE	P value
1	Mean Brachial Diameter	-1.18	0.31	< 0.001
	Age	-0.05	0.02	0.026
	Sex (F)	0.15	0.47	0.752
	MetS	-0.41	0.35	0.241
2	Mean Brachial Diameter	-1.23	0.30	< 0.001
	Age	-0.04	0.02	0.039
	Sex (F)	0.01	0.46	0.977
	$\log_2$(AHI+1)	-0.16	0.12	0.171
3	Mean Brachial Diameter	-1.17	0.31	< 0.001
	Age	-0.04	0.02	0.041
	Sex (F)	0.11	0.47	0.810
	MetS	-0.29	0.37	0.421
	$\log_2$(AHI+1)	-0.13	0.12	0.284
4	Mean Brachial Diameter	-1.15	0.31	< 0.001
	Age	-0.05	0.02	0.023
	Sex (F)	0.12	0.47	0.793
	MetS	1.40	0.75	0.064
	$\log_2$(AHI+1)	0.09	0.15	0.540
	$\log_2$(AHI+1) * MetS	-0.64	0.25	0.011
5	Mean Brachial Diameter	-1.15	0.33	< 0.001
	Age	-0.05	0.02	0.028
	Sex (F)	0.13	0.51	0.795
	Current Smoker	0.19	0.54	0.721
	BMI	-0.00	0.03	0.934
	MetS	1.42	0.77	0.066
	$\log_2$(AHI+1)	0.09	0.15	0.538
	$\log_2$(AHI+1) * MetS	-0.64	0.25	0.011

AHI, apnea-hypopnea index; BMI, body mass index; FMD, flow-mediated dilation; MetS, metabolic syndrome; SE, standard error.

Table 3—Multivariable models of FMD by metabolic syndrome status as predicted by AHI.

		Metabolic Syndrome Status					
		Status = No (n = 279)			Status = Yes (n = 152)		
		β Estimate	SE	P value	β Estimate	SE	P value
1	Mean Brachial Diameter	-1.15	0.37	0.002	-1.19	0.56	0.035
	Sex (F)	0.15	0.57	0.797	0.10	0.83	0.906
	Age	-0.07	0.03	0.008	-0.01	0.04	0.711
	$\log_2$(AHI+1)	0.12	0.15	0.414	-0.56	0.21	0.009
2	Mean Brachial Diameter	-1.14	0.40	0.005	-1.19	0.59	0.045
	Sex (F)	0.17	0.62	0.781	0.11	0.93	0.906
	Age	-0.07	0.03	0.010	-0.01	0.03	0.766
	Current Smoker	0.10	0.64	0.879	0.47	1.07	0.664
	BMI	-0.01	0.04	0.906	-0.00	0.05	0.970
	$\log_2$(AHI+1)	0.13	0.16	0.418	-0.55	0.22	0.014

AHI, apnea-hypopnea index; BMI, body mass index; SE, standard error.

Table 4—Multivariable models of FMD by metabolic syndrome status as predicted by AHI categories.

	MetS (ref: no-MetS) beta (SE)	P-value	Interaction Term P-value
AHI 0–4.9	0.90 (0.60)	0.134	Ref
AHI 5–14.9	-1.02 (0.64)	0.110	0.181
AHI ≥ 15	-2.90 (0.97)	0.005	0.002

Test for trend interaction term between MetS and categorical AHI P = 0.003. AHI, apnea-hypopnea index; MetS, metabolic syndrome; SE, standard error.

circumference) or HOMA-IR, the interaction terms between logAHI and the individual risk factors for MetS were not significant (data not shown).

DISCUSSION

MetS and SDB share many features and both are associated with increased CVD risk,[2,3]making it difficult to assess the individual impact of these conditions on CVD risk. In our study, brachial artery endothelial function was used as a marker of cardiovascular health. As expected, subjects with MetS had greater AHI and worse FMD than those without MetS, although neither higher AHI nor MetS alone were independently associated with endothelial dysfunction in our population; the interaction between AHI * MetS was a significant predictor. This suggests that the combined effects of both disease processes have a significant deleterious effect on endothelial function. Analyses restricted to subjects with MetS showed that AHI independently predicted FMD. As expected, insulin resistance was significantly associated with waist, but the association was even stronger among subjects with severe SDB.

Subjects with the combination of SDB and MetS have repeated hypoxic events and increased sympathetic tone[29] and release of reactive oxygen species, which could secondarily lead to loss of endothelial function, poor glycemic control, blood pressure elevation, and higher cholesterol levels.[30] Still, previous clinical studies have looked at the combined effects of SDB and MetS in endothelial function, with mixed results. Amra et al. found that endothelial function was not different among SDB subjects with or without MetS.[31] These results might be due to the study's small sample size and varying degrees of SDB severity.

Obese subjects with SDB have higher levels of circulating leptin compared to matched obese controls and tend to gain more weight over time.[32] In large epidemiological studies,[33] glucose intolerance has been associated with SDB severity independent of age, gender, BMI, or waist circumference. SDB also leads to elevated fasting insulin levels independent of BMI or other measures of obesity.[34] Treatment of SDB patients with CPAP significantly lowered leptin levels and decreased visceral and subcutaneous fat after 6 months of use, suggesting that deposition of central adipose tissue could be mediated through metabolic derangements that are directly caused by SDB. A group of individuals with severe SDB and metabolic syndrome on CPAP had significant improvement in blood pressure, insulin resistance, total cholesterol, TNF-α, and oxidative stress markers after 8 weeks of treatment.[35]

Finally, a recent randomized crossover study of healthy young adults showed that sleep restriction resulted in increased insulin resistance.[36] The link between insomnia and abnormal glucose metabolism might explain why AHI (which is a marker of *both* sleep arousals—poor sleep quality and intermittent hypoxemia) resulted in a better predictor of insulin resistance and endothelial dysfunction than mean nocturnal O_2 saturation in the current study.

Limitations

The PSG studies were recorded on average 1.6 years before the FMD and metabolic assessment visits. Ideally these could have been closer to each other, but based on SDB progression rates in the cohort and other studies; we believe this time span without significant changes in body mass index is not enough to expect significant differences in AHI results and SDB severity.[37,38]

The overall SDB severity in this sample was mild (mean AHI 7.1 [8.6]); however, the associations we found likely would be even stronger if we had participants with more severe SDB. As expected in a population study, in our study the moderate-to-severe SDB group without MetS was the smallest (only 19 participants); and thus we may have lacked enough statistical power to detect an independent association between SDB and FMD. Use of antihypertensive and lipid-lowering therapy was common in the study population and may have diminished associations among SDB, MetS, and FMD. As a cross-sectional, observational study, we did not account for duration of SDB, length of MetS diagnosis, and chronic exposure to other CVD risk factors. Longitudinal evaluation of these parameters could provide a better insight on individual effects and timing for the development of endothelial dysfunction. Lastly, the effect of CPAP therapy in insulin resistance and endothelial function could not be analyzed in this study. Lack of objective CPAP compliance information and length of use precluded us from accurately assessing the effect of CPAP therapy on endothelial function.

There is the possibility that our findings represent a false positive, and the replication of these results in other studies is needed before a firm conclusion is reached.

CONCLUSIONS

Among individuals with MetS, the presence of SDB is associated with worse endothelial function. The significant interaction between AHI and MetS suggests that combined effects of MetS and SDB have a worse impact on endothelial function and synergistically increase CVD risk. Diagnosis and treatment of SDB also should address the metabolic derangements of MetS to result in a more effective treatment for these often concomitant conditions.

ABBREVIATIONS

AHI, apnea-hypopnea index
BART, brachial artery reactivity testing
CVD, cardiovascular disease
DM, diabetes mellitus
FMD, flow-mediated dilation
HOMA-IR, homeostatic model assessment-insulin resistance
MetS, metabolic syndrome
SDB, sleep disordered breathing

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