ORIGINAL RESEARCH

Sex-Specific Association of Obstructive Sleep Apnea With Retinal Microvascular Signs: The Multi-Ethnic Study of Atherosclerosis

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***Background*—**Obstructive sleep apnea (OSA) is a common condition affecting more men than women. The relationship of OSA with microvascular disease is unclear, complicated by possible sex difference. Assessment of the relationship of OSA with retinal microvascular signs in men and women may provide insights into such a relationship.

***Methods and Results*—**We examined the sex-specific cross-sectional association of OSA severity with retinal vascular calibers in 1808 participants, and with specific retinopathy signs in 1831 participants from a sample of 2060 participants aged 54 to 93 years who underwent successful polysomnography in the Multi-Ethnic Study of Atherosclerosis, 2010–2012. OSA severity was defined by the apnea–hypopnea index (events/h) as none (<5), mild (5–14.9), moderate (15–29.9), and severe (≥30). As compared to no OSA, moderate/severe OSA in men was associated with retinal arteriolar narrowing (odds ratio [OR] and 95% CI for the narrowest quartile: 1.65 [1.00–2.71]) and retinal venular widening (1.80 [1.07–3.04] for the widest quartile), but not in women (odds ratio: 1.10 [0.67–1.81] and 0.91 [0.58–1.43], respectively) after adjusting for age, race/ethnicity, body mass index, pack-years of cigarette smoking, alcohol intake, hypertension duration, diabetes mellitus duration, HbA1c levels, lipid profile, micro-/macroalbuminuria, estimated glomerular filtration rate, β-blockers use, antihypertensive therapy, and lipid-lowering therapy. In contrast, severe OSA was associated with retinal microaneurysms in women, but not in men (odds ratio: 3.22 [1.16–8.97] and 0.59 [0.27–1.30], respectively).

***Conclusions*—**The associations of OSA severity with retinal microvascular signs may differ by sex. Whether these findings were related to sex differences in OSA exposure needs further investigation. **(*J Am Heart Assoc*. 2016;5:e003598 doi: 10.1161/JAHA.116.003598)**

Key Words: apnea-hypopnea index • epidemiology • microvascular dysfunction • obstructive sleep apnea • retinal vascular calibers • retinopathy • sex-specific

Obstructive sleep apnea (OSA), a common condition in older adults affecting more males than females,[1] causes intermittent nocturnal hypoxemia and is associated with inflammation, metabolic abnormalities, endothelial dysfunction, and poor control of diabetes mellitus and hypertension, which may lead to micro- and macrovascular disease.[2–4] OSA has been associated with higher risk of clinical cardiovascular disease (CVD), including ischemic stroke and coronary heart disease, independent of traditional risk factors and severity of atherosclerosis.[4,5] It is unknown whether this relationship is related to microvascular disease.[6,7] Some investigators have suggested microvascular disease may be a potential mediator for the association between OSA and clinical CVD. However, current evidence for the association of OSA with microvascular disease is conflicting. Some brain imaging studies revealed inconsistent results for the association between OSA and cerebral small-vessel disease.[8,9] In addition, although some cardiac perfusion scans showed that OSA is associated

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with impaired myocardial microcirculation in patients with acute myocardial infarction, this finding may be attributable to the production of lipid microemboli from atheroma plaque rupture.[10,11]

The retinal microvasculature is structurally and functionally similar to microvasculature elsewhere in the body.[12] Previous studies have demonstrated the relationship between retinal microvascular signs and cardiovascular risk factors and shown that these signs predict a range of CVD, including stroke, coronary heart disease, and congestive heart failure.[13,14] Retinal arteriolar narrowing is strongly related to hypertension and age,[15] while retinal venular widening is related to cigarette smoking, inflammation, atherosclerosis, and metabolic abnormalities such as obesity, hyperglycemia, and diabetes mellitus.[13,16] Retinopathy signs, specifically microaneurysms, hemorrhages, and cotton wool spots found in patients with diabetes mellitus are also prevalent in the general population (5% to 10%), and may be related to age, obesity, hyperglycemia, inflammation, and elevated blood pressure (BP).[13]

Several retinal imaging studies have been used to evaluate the association between sleep-disordered breathing and retinal microvascular signs.[17–21] These studies showed conflicting results. Notably, results from a recent analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) data visit 2 (2002–2004), in which a sample of 5803 participants underwent both a self-administered sleep history questionnaire and retinal photography, found that physician-diagnosed sleep apnea (PDSA) was associated with retinal arteriolar narrowing in women only.[21] There was no association between PDSA and retinal vascular calibers in men. The clinical course of OSA differs between men and women with women on average having less severe sleep apnea than men at younger ages, with differences narrowing after menopause.[22] Prior research suggests a sex difference in the associations between OSA and clinical CVD.[23] Therefore, the association between OSA and retinal microvascular signs may differ by sex. Since PDSA was not an objective measure of OSA severity in the previous MESA study,[21] we used rigorously collected data from polysomnography (PSG) and retinal photography in a large multi-ethnic general population in the MESA visit 5 (2010–2012) to quantify the sex-specific association between OSA and retinal microvascular signs.

Methods

Study Population and Data Collection

The study design for MESA has been published elsewhere.[24] In brief, MESA is a longitudinal cohort study designed to investigate the prevalence, correlates, and progression of subclinical CVD in individuals without clinical CVD at baseline. The cohort includes 6814 women and men aged 45–84 years old recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN) at the baseline examination (July 2000–July 2002). The participants were 38% white, 28% African American, 22% Hispanic, and 12% Chinese. This study was approved by the Institutional Review Board of each study site, and written informed consent was obtained from all participants.

In conjunction with the fifth MESA examination (April 2010–February 2012), all MESA participants were offered fundus photography, and except for those reporting regular use of oral devices, nocturnal oxygen, or nightly positive airway pressure devices, all participants were also invited to participate in the MESA Sleep Ancillary Study, which included in-home PSG. Of 4077 participants approached for PSG, 147 (3.6%) were ineligible and 141 lived too far away to participate. Of the remaining 3789 participants, 2261 participated in the sleep exam (59.7%) and 2060 had successful PSG data. We further excluded those with poor retinal image quality in both eyes, and those with missing data on relevant variables, leaving a sample of 1808 individuals (87.8%) aged 54 to 93 years for the analysis of retinal vascular calibers and another sample of 1831 individuals (88.9%) for the analysis of retinopathy signs (Figure).

PSG and OSA Definition

A 15-channel PSG recording (Compumedics Somte® System; Compumedics Ltd., Abbotsville, AU) including electroencephalography, electrooculography, chin electromyography, oxyhemoglobin saturation (finger pulse oximetry), chest and abdominal excursion (inductance plethysmography), airflow (oral and nasal thermocouple), leg movements, body position, and ambient light was taken in the participant's home. The PSG data were transmitted to the centralized reading center in the Brigham and Women's Hospital (Boston, MA) for review and scoring by a certified polysomnologist masked to all other data. Sleep stages and electroencephalography (cortical) arousals were scored based on published guidelines and adapted for unattended studies using methods from the Sleep Heart Health Study, as detailed.[25] Apnea was scored when the thermocouple signal flattened or nearly flattened for >10 s. Hypopnea was scored if the amplitude of the sum of the abdominal and thoracic inductance signals or the nasal pressure flow signal decreased by 30% or more for ≥10 s. Apneas were classified as "obstructive" or "central" based on absence or presence of respiratory effort during the event. Specialized software was used to link apnea and hypopnea with data from the oxygen saturation and electroencephalography signals, allowing each event to be characterized according to the degree of associated desaturation and arousal. In this analysis, the primary exposure variable was

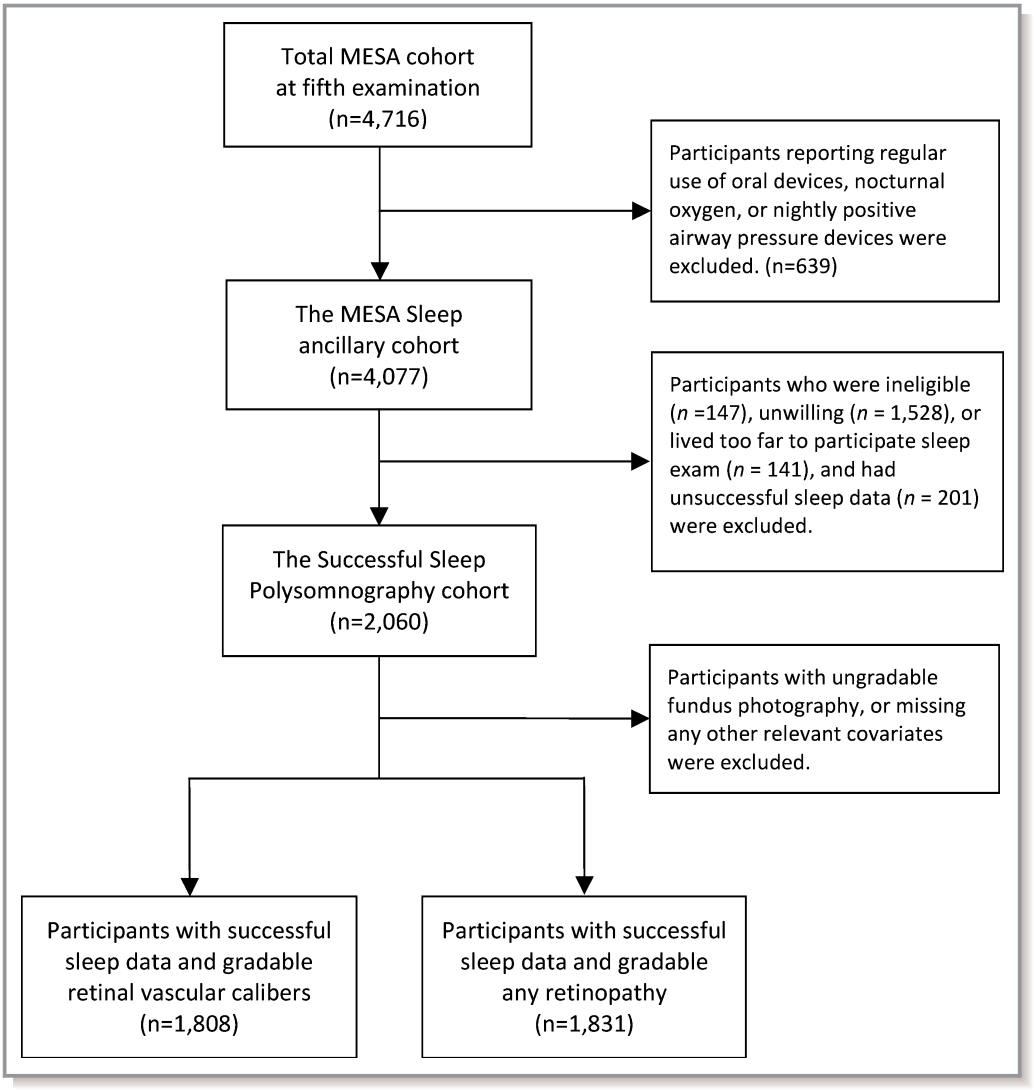

Figure. Flow diagram to select the eligible MESA sleep-eye cohort, 2010–2012. MESA indicates Multi-Ethnic Study of Atherosclerosis.

the apnea–hypopnea index (AHI) defined as the average number of obstructive apneas plus hypopneas associated with a ≥4% desaturation per hour of objectively measured sleep.[26] Intraclass correlation coefficients for within- and between-scorer reliability exceed 0.94.

Retinal Photography and Retinal Grading

Fundus photography was performed in both eyes of each participant according to a standardized protocol using a 45° digital nonmydriatic camera.[27] All images were sent to the Ocular Epidemiology Reading Center at the University of Wisconsin (Madison, WI) and were evaluated by trained graders masked to participants' characteristics. Retinopathy was considered present if the graders found any lesions as defined by the Early Treatment Diabetic Retinopathy Study severity scale, including retinal hemorrhages, microaneurysms, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, retinal neovascularization, and other lesions of proliferative diabetic retinopathy.[28] Retinal vascular caliber was measured with a computer-based program following a detailed protocol.[28] For each photograph, all retinal arterioles and venules coursing through a zone between 0.5- and 1-disc diameter away from the optic disc margin were measured as the central retinal arteriolar equivalents and venular equivalents.[29,30] The average of the right and left eye measurements was taken for both central retinal arteriolar equivalents and central retinal venular equivalents in each participant. If retinal vascular diameter could not be measured in both eyes, the eye with the available photograph was used. The reproducibility of retinal vascular measurements has been reported previously with intra- and intergrader intraclass correlation coefficients ranging from 0.78 to 0.99.[14,15]

Assessment of Risk Factors for OSA and Retinal Microvascular Signs

All participants underwent an interview and were assessed for CVD risk factors at the fifth examination. Risk factors related to OSA or retinal microvascular signs were defined as follows. Body mass index (BMI) was calculated as weight (kg)/height squared (m^2). Smoking status was defined as current, former, and never. Pack-years of cigarette smoking were estimated from age of starting to quitting (or current age among current smokers)×(cigarettes per day/20). Alcohol intake was classified into current and not current drinking. BP was ascertained as the mean of the last 2 of 3 seated measurements. Hypertension was defined as systolic BP ≥140 mm Hg, or diastolic BP ≥90 mm Hg, or use of antihypertensive medication. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL or the use of hypoglycemic medications. HbA1c was measured on the Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, Inc, Hercules, CA) using automated high-performance liquid chromatography. Glomerular filtration rate was estimated according to the Chronic Kidney Disease Epidemiology Collaboration equation.[31] Micro- and macroalbuminuria were defined by urinary albumin–creatinine ratios of 30 to 299 mg/g and ≥300 mg/g, respectively. Total cholesterol and high-density lipoprotein cholesterol were measured from blood samples obtained after a 12-hour fast. Medication use was assessed by reviewing participants' medication containers.

Statistical Analysis

The severity of OSA was classified by AHI (events/h) as none (<5), mild (5–14.9), moderate (15–30), and severe (≥30). Demographic characteristics of participants in each of the OSA groups were compared using either χ^2 analysis or ANOVA and reported as mean±SD or percent for continuous and categorical variables, respectively. The effect of OSA severity on retinal vascular calibers was estimated by using ANCOVA, and the results were presented as means and SE of retinal arteriolar and venular calibers for men and women. The overall effect of OSA severity was tested and in the presence of a significant overall test, pairwise comparisons of no OSA with mild and with moderate/severe OSA were performed, respectively. Initial models constructed using ANCOVA were adjusted for age and race/ethnicity.

Logistic regression was used to determine the odds of retinal arteriolar narrowing (the narrowest quartile versus others), retinal venular widening (the widest quartile versus others), and specific retinopathy signs in association with OSA severity in men and women. The Wald χ^2 test from the type 3 analysis of effects was used to determine the overall significance of OSA severity. Linear regression was also used to determine the associations of OSA with retinal arteriolar and venular calibers in men and women. In comparison with the categorical OSA severity, we analyzed the linear association of AHI with retinal vascular caliber by AHI: 0 to 14.9 (none-to-mild OSA) and AHI ≥15 (moderate-to-severe OSA) in a piecewise fashion. We constructed 3 models: model 1 included adjustments for age and race/ethnicity; model 2 included additional adjustments for BMI, systolic BP, diabetes mellitus status, serum total cholesterol, high-density lipoprotein cholesterol, smoking status, alcohol intake, antihypertensive therapy, and lipid-lowering therapy. Model 3 included comprehensive adjustments for age, race/ethnicity, BMI, pack-years of cigarette smoking, alcohol intake, duration of hypertension and diabetes mellitus (duration was defined as none, longer, or shorter than an average 9.5-year period between the first and the fifth visit of MESA), HbA1c, total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, micro-/macroalbuminuria, antihypertensive therapy, medication with β-blockers, lipid-lowering therapy, and current hormone replacement therapy (for women only). Models predicting retinal arteriolar caliber were adjusted for venular caliber and vice versa. These potential confounders in models were chosen based on prior published associations with OSA or retinal microvascular signs.[32–34] Formal testing for interactions between men and women regarding the associations of OSA severity with retinal microvascular signs was performed. Exploratory analyses were conducted examining associations for specific retinopathy signs in men and women. A 2-tailed value of $P<0.025$ was considered significant for the overall test of OSA severity in men and women separately. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

The baseline characteristics of the study cohort shown by severity of OSA in men and women are provided in Table 1. As compared to those with no OSA, those with mild or moderate or severe OSA were older and had greater proportions of those with obesity, hypertension, diabetes mellitus, dyslipidemia, and CVD. OSA was more common in men than in women.

Mild OSA was found in 31.7% and 32.3% of men and women, respectively, whereas moderate/severe OSA occurred in 43.0% of men and 23.2% of women (Table 2). As compared with those with no OSA, the mean value of retinal arteriolar caliber was significantly smaller in men but not in women with OSA. In contrast, the mean value of retinal venular caliber was greater in both men and women with more severe OSA.

Table 1. Characteristics of the Population by the Severity of OSA Estimated by AHI in Men and Women

	Men			Women		
	No OSA (AHI: <5)	Mild OSA (AHI: 5–14.9)	Moderate/Severe OSA (AHI: ≥15)	No OSA (AHI: <5)	Mild OSA (AHI: 5–14.9)	Moderate/Severe OSA (AHI: ≥15)
Sample size	222	279	383	440	321	229
Age, y	66.7±8.6	68.8±9.1	68.8±9.2	66.4±8.9	69.8±9.0	68.3±8.5
Race/ethnicity (%)						
White	39.6	41.6	30.8	38.9	35.5	31.9
Black	30.6	22.2	25.3	25.9	28.7	29.3
Hispanic	18.5	25.1	26.9	22.1	24.3	28.8
Chinese	11.3	11.1	17.0	13.2	11.5	10.0
BMI, kg/m^2	26.4±3.9	27.8±3.7	29.4±5.1	26.8±5.4	29.5±5.9	32.4±6.4
Diabetes mellitus (%)	15.3	18.6	24.5	13.0	17.5	29.7
Systolic BP, mm Hg	120.2±20.6	121.2±18.6	122.7±18.2	119.7±20.5	125.1±20.1	125.3±21.2
Diastolic BP, mm Hg	70.8±9.7	70.5±9.6	71.6±9.7	65.4±9.5	66.4±9.4	66.1±9.5
Antihypertensive therapy (%)	46.0	50.5	55.9	45.7	57.3	60.3
Total cholesterol, mg/dL	172.3±35.0	173.3±33.5	172.1±36.2	196.7±34.0	192.8±34.8	189.4±36.2
HDL-C, mg/dL	52.3±15.4	49.4±13.5	48.0±12.0	63.4±17.9	59.7±15.5	56.3±15.4
LDL-C, mg/dL	100.9±32.2	102.4±29.6	100.1±32.1	112.7±30.9	111.0±32.1	110.0±33.5
Triglycerides, mg/dL	97.9±59.6	109.7±69.1	121.9±80.7	104.6±59.6	110.5±53.8	115.2±50.8
Lipid-lowering therapy (%)	33.8	40.9	42.0	30.5	37.4	43.7
Smoking status (%)						
Current/former/never	8.1/53.2/38.7	10.4/53.1/36.6	5.5/55.4/39.2	7.3/35.5/57.3	5.6/40.5/53.9	5.2/40.6/54.2
Alcohol drinking status (current, %)	53.2	51.6	49.6	38.4	36.8	36.7
Hormone replacement therapy (current, %)	—	—	—	8.2	6.2	5.2
AHI, events/h, median (25th, 75th percentile)	2.0 (1.0, 3.1)	9.4 (6.8, 12.2)	29.1 (20.0, 43.3)	1.9 (0.8, 3.4)	9.1 (6.6, 11.6)	24.3 (18.7, 37.3)
Cardiovascular disease (%)	5.9	7.5	7.6	4.1	5.3	4.4

AHI indicates apnea–hypopnea index (events/h); BMI, body mass index; BP, blood pressure; HDL-C, high-density lipo protein cholesterol; LDL-C, low-density lipoprotein cholesterol; OSA, obstructive sleep apnea.

Table 3 shows the results of the logistic regression model of the relationship of mild and moderate/severe OSA with retinal arteriolar narrowing and retinal venular widening as compared with no OSA in men and women. After adjusting for age and race/ethnicity, mild and moderate/severe OSA were associated with increased odds of retinal arteriolar narrowing in men (odds ratios [OR]: 2.26 and 1.91, and overall *P* value: 0.003), but not in women. After additionally adjusting for BMI, systolic BP, diabetes mellitus status, total cholesterol, high-density lipoprotein cholesterol, smoking status, alcohol intake, antihypertensive therapy, and lipid-lowering therapy, the overall OSA association remained significant (*P*=0.014): mild OSA was significant (OR: 2.08, *P*=0.006) and moderate/severe OSA was marginally significant (OR: 1.66, *P*=0.052) for retinal arteriolar narrowing in men. The overall OSA association was not significant in women (overall *P*=0.87, OR: 0.95 and 1.09, respectively; *P* value for interaction of sex: 0.06).

The associations between OSA severity and retinal vascular calibers for men and women were consistent in the model 3 linear regression analyses despite the *P* values for interaction of sex being not significant (Table 4). Notably, AHI levels were linear inversely associated with retinal arteriolar calibers in men only if AHI <15, the maximal threshold of mild OSA (β=−0.25, *P*: 0.034, Table 5), in model 3. On the contrary, AHI levels were not associated with retinal vascular calibers in women (Table 5). Table 6, the exploratory analysis, shows that severe OSA was associated with higher risk of retinal microaneurysms in women in model 3 (OR: 3.22 and *P* value: 0.025). In addition, severe OSA was marginally associated with retinal arteriovenous nicking and soft exudates (OR: 1.61 [95% CI: 0.99–2.60] and 2.80 [95% CI: 0.99–7.92], and *P* values: 0.053 and 0.054, respectively; data not shown) in women in model 1; however, the associations were attenuated and became nonsignificant after adjusting for traditional

Table 2. Relationship of OSA Severity With Retinal Vascular Calibers

	N (%)	Retinal Arteriolar Caliber, μm Mean (SE)	Retinal Venular Caliber, μm Mean (SE)
Men (N=848)			
No OSA	214 (25.2)	141.2 (0.74)	203.6 (1.16)
Mild OSA	269 (31.7)	138.3 (0.67)	206.8 (1.03)
Moderate/severe OSA	365 (43.0)	138.6 (0.56)	208.0 (0.87)
Overall *P* value		0.004	0.007
P value for mild OSA vs no OSA		0.003	0.03
P value for moderate/severe OSA vs no OSA		0.004	0.002
Women (N=960)			
No OSA	427 (44.5)	144.3 (0.56)	206.1 (0.82)
Mild OSA	310 (32.3)	143.0 (0.65)	208.2 (0.95)
Moderate/severe OSA	223 (23.2)	142.9 (0.76)	209.9 (1.11)
Overall *P* value		0.20	0.015
P value for mild OSA vs no OSA		0.14	0.09
P value for moderate/severe OSA vs no OSA		0.13	0.005
P value for interaction of sex		0.44	0.86

Mean (SE) for retinal vascular caliber estimated using analysis of covariance with adjustments for age, race/ethnicity, and fellow retinal vascular caliber (μm). OSA indicates obstructive sleep apnea.

vascular risk factors, BMI and diabetes mellitus status. The associations of severe OSA with retinal microaneurysms, arteriovenous nicking, and soft exudates in men were reversed but nonsignificant in model 3 (OR: 0.59, 0.78, and 0.87, respectively).

Discussion

Our principal finding was that mild and moderate/severe OSA was associated with narrower retinal arterioles, and moderate/severe OSA was associated with wider retinal venules in

Table 3. Logistic Regression of Retinal Vascular Calibers by OSA Severity

	Retinal Arteriolar Narrowing*			Retinal Venular Widening†		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Men						
Mild OSA	2.26‡ (1.40–3.64)	2.08‡ (1.27–3.41)	2.00‡ (1.22–3.29)	1.57 (0.94–2.61)	1.38 (0.82–2.34)	1.48 (0.87–2.54)
Moderate/severe OSA	1.91‡ (1.20–3.04)	1.66§ (1.01–2.72)	1.65 (1.00–2.71)	1.99‡ (1.24–3.20)	1.71§ (1.03–2.84)	1.80§ (1.07–3.04)
Overall *P* value	0.003	0.014	0.024	0.016	0.12	0.09
Women						
Mild OSA	1.03 (0.68–1.57)	0.95 (0.61–1.47)	0.95 (0.61–1.48)	1.28 (0.89–1.85)	1.07 (0.72–1.57)	1.08 (0.73–1.59)
Moderate/severe OSA	1.27 (0.80–2.02)	1.09 (0.66–1.80)	1.10 (0.67–1.81)	1.22 (0.82–1.82)	0.91 (0.58–1.42)	0.91 (0.58–1.43)
Overall *P* value	0.57	0.87	0.86	0.37	0.81	0.74
P value for interaction of sex	0.06	0.06	0.07	0.25	0.16	0.14

Data shown are odds ratios (95% CI). The reference group was no OSA. Model 1: odds ratio adjusted for age and race. Model for arteriolar caliber was adjusted for venular caliber, and vice versa. Model 2: model 1 plus further adjustments for systolic blood pressure, antihypertensive therapy, body mass index, diabetes mellitus, total and high-density lipoprotein cholesterol, lipid-lowering therapy, cigarette smoking status, and alcohol intake status. Model 3: model 1 plus further adjustments for body mass index, duration of hypertension and diabetes mellitus (longer or shorter than an average 9.5-year period between MESA visit 1 and 5), HbA1c, pack-years cigarette smoking, alcohol status, estimated glomerular filtration rate, micro-/macroalbuminuria, antihypertensive therapy, β-blocker medication, total and high-density lipoprotein cholesterol, lipid-lowering therapy, and current hormone replacement therapy (for women only). MESA indicates Multi-Ethnic Study of Atherosclerosis; OSA, indicates obstructive sleep apnea.

*Retinal arteriolar narrowing was defined as the narrowest quartile of retinal arteriolar calibers in the overall cohort.

†Retinal venular widening was defined as the widest quartile of retinal venular calibers in the overall cohort.

‡$P<0.025$.

§$P<0.05$.

Table 4. Linear Regression Model of OSA Severity With Retinal Vascular Calibers in Men and Women

	Men		Women		*P* Value for Interaction of Sex
	β (SE)	*P* Value	β (SE)	*P* Value	
Retinal arteriolar caliber, μm					
Mild OSA	−2.58 (0.99)	0.009	−0.88 (0.86)	0.31	0.37
Moderate/severe OSA	−2.09 (0.97)	0.032	−0.90 (1.00)	0.37	
Overall *P* value		0.027		0.53	
Retinal venular caliber, μm					
Mild OSA	2.36 (1.53)	0.12	0.96 (1.25)	0.44	0.59
Moderate/severe OSA	2.76 (1.51)	0.067	2.05 (1.45)	0.16	
Overall *P* value		0.016		0.36	

Linear regression model adjusted for age, race, body mass index, duration of hypertension and diabetes mellitus (longer or shorter than an average 9.5-year period between MESA visit 1 and visit 5), HbA1c, pack-years cigarette smoking, alcohol status, estimated glomerular filtration rate, micro-/macroalbuminuria, antihypertensive therapy, β-blockers medication, total and high-density lipoprotein cholesterol, lipid-lowering therapy, and current hormone replacement therapy (for women only). Model for retinal arteriolar caliber was adjusted for retinal venular caliber, and vice versa. AHI indicates apnea–hypopnea index; MESA, Multi-Ethnic Study of Atherosclerosis; OSA, obstructive sleep apnea.

men. However, there was no association between OSA severity and retinal vascular calibers in women. In contrast, in exploratory analyses the association of severe OSA with retinal microaneurysms was greater in women than men. The sex-specific OSA associations with retinal vascular calibers and retinopathy were independent of BMI and traditional CVD risk factors: age, hypertension and diabetes mellitus status (severity and duration), lipid profile, cigarette smoking status, alcohol intake, micro/macroalbuminuria, renal function, and medications.

Two cross-sectional studies have examined the association between sleep-disordered breathing and retinal vascular signs in the general population. In the Sleep Heart Health Study,[17] Boland et al reported no association between AHI and most retinal microvascular abnormalities, with the exceptions of an association with microaneurysms and smaller retinal arteriole-to-venule ratio, where the inverse linear relationship was blunted when the AHI was >10. In the Wisconsin Sleep Cohort Study,[18] Shankar et al subsequently reported that moderate/severe sleep-disordered breathing (AHI ≥15) was associated with retinal venular widening, but not with retinal arteriolar narrowing in men or women. Reports on the association of OSA with retinopathy in diabetic populations have been inconsistent. Rudrappa et al showed that OSA may promote diabetic retinopathy, whereas Banerjee et al reported no association.[19,20] In line with Sleep Heart Health Study and Wisconsin Sleep Cohort Study,[17,18] our analysis revealed a nonlinear inverse association between AHI and retinal arteriolar calibers, an association between moderate/severe OSA and retinal venular widening in men, and an association between severe OSA with retinal microaneurysms in women.

Those findings from the earlier study in MESA appear to contradict the present study results.[21] Although PDSA may be a useful surrogate for more severe OSA in MESA,[35] it is likely those with unrecognized OSA might be misclassified to the unaffected group. In fact, the median AHI levels, obtained by

Table 5. Linear Regression Model of AHI With Retinal Vascular Calibers in Men and Women

	Men		Women		*P* Value for Interaction of Sex
	β (SE)	*P* Value	β (SE)	*P* Value	
Retinal arteriolar caliber, μm					
AHI <15 events/h	−0.25 (0.12)	0.034	−0.048 (0.10)	0.64	0.12
AHI ≥15 events/h	0.020 (0.034)	0.55	0.038 (0.055)	0.49	0.77
Retinal venular caliber, μm					
AHI <15 events/h	0.039 (0.17)	0.82	0.11 (0.15)	0.47	0.72
AHI ≥15 events/h	−0.044 (0.057)	0.44	−0.060 (0.076)	0.44	0.90

Linear regression model adjusted for age, race/ethnicity, body mass index, duration of hypertension and diabetes mellitus (none, longer or shorter than an average 9.5-year period between MESA visit 1 and visit 5), HbA1c, pack-years cigarette smoking, alcohol status, estimated glomerular filtration rate, micro-/macroalbuminuria, antihypertensive therapy, β-blockers medication, total and high-density lipoprotein cholesterol, lipid-lowering therapy, and current hormone replacement therapy (for women only). Model for retinal arteriolar caliber was adjusted for retinal venular caliber, and vice versa. AHI indicates apnea–hypopnea index; MESA, Multi-Ethnic Study of Atherosclerosis.

Table 6. Logistic Regression Models Comparing OSA Severity Against No OSA by Specific Retinopathy Sign, Separately in Men and Women

	Men				Women			
	Mild OSA	Moderate OSA	Severe OSA	Overall *P* Value	Mild OSA	Moderate OSA	Severe OSA	Overall *P* Value
Retinal microaneurysm*								
Model 3	0.70 (0.36–1.36)	0.69 (0.34–1.39)	0.59 (0.27–1.30)	0.55	1.07 (0.49–2.36)	0.99 (0.35–2.85)	3.22 (1.16–8.97)†	0.11
Retinal blot hemorrhages*								
Model 3	0.62 (0.18–2.19)	0.39 (0.09–1.72)	0.65 (0.16–2.62)	0.66	0.70 (0.30–1.61)	0.96 (0.37–2.53)	0.43 (0.08–2.14)	0.66
Retinal soft exudate*								
Model 3	0.68 (0.18–2.49)	0.55 (0.14–2.21)	0.87 (0.23–3.26)	0.63	0.84 (0.30–2.38)	1.74 (0.60–5.08)	1.64 (0.47–5.70)	0.50
Retinal arteriovenous nicking*								
Model 3	0.99 (0.67–1.46)	1.01 (0.66–1.55)	0.78 (0.49–1.24)	0.63	0.99 (0.71–1.38)	0.97 (0.63–1.50)	1.57 (0.93–2.65)	0.32
Retinal focal arteriolar narrowing*								
Model 3	0.64 (0.24–1.72)	0.70 (0.24–2.10)	0.86 (0.29–2.58)	0.82	NE	NE	NE	NA
Any retinopathy sign*‡								
Model 3	0.62 (0.34–1.13)	0.58 (0.31–1.11)	0.69 (0.36–1.35)	0.32	1.19 (0.67–2.10)	1.03 (0.49–2.16)	2.14 (0.96–4.77)	0.29

Data shown are odds ratios (95% CI). The reference group was no OSA. Model 1: odds ratio adjusted for age and race. Model for arteriolar caliber was adjusted for venular caliber, and vice versa. Model 2: model 1 plus further adjustments for systolic blood pressure, antihypertensive therapy, body mass index, diabetes mellitus, total and high-density lipoprotein cholesterol, lipid-lowering therapy, cigarette smoking status, and alcohol intake status. Model 3: model 1 plus further adjustments for body mass index, duration of hypertension and diabetes mellitus (longer or shorter than an average 9.5-year period between MESA visit 1 and 5), HbA1c, pack-years cigarette smoking, alcohol status, estimated glomerular filtration rate, micro-/macroalbuminuria, antihypertensive therapy, β-blocker medication, total and high-density lipoprotein cholesterol, lipid-lowering therapy, and current hormone replacement therapy (for women only). MESA indicates Multi-Ethnic Study of Atherosclerosis; NA, not available; NE, not estimable; OSA, obstructive sleep apnea.

**P*-value for interaction of sex for retinal microaneurysms: 0.09, blot hemorrhages: 0.56, soft exudate: 0.45, arteriovenous nicking: 0.20, focal arteriolar narrowing: 0.56, and any retinopathy sign: 0.13.

†*P*=0.025.

‡Any retinopathy sign included retinal hemorrhages, microaneurysms, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, retinal neovascularization, or other lesions of proliferative diabetic retinopathy.

the PSG in the MESA visit 5 for men self-reporting in MESA visit 2 as unaffected, habitual snoring, and PDSA, were 10.8, 15.3, and 25.9, respectively. More than half of the men self-reporting that they were unaffected at visit 2 actually had OSA when objectively measured by PSG at visit 5. Since the association of OSA with retinal arteriolar calibers was not dose dependent in men, a negative result using self-report data may be erroneous and a direct result of OSA misclassification in the reference group. Furthermore, unrecognized sleep apnea may be more common in women, in whom a PDSA may identify the most severely affected individuals. In contrast to the 70 women with PDSA by self-report at MESA visit 2 (2.3% of the total female cohort in the prior MESA analysis), in the present study, there were 87 women with severe OSA and 229 women with moderate or severe OSA, accounting for 8.8% and 23.1% of the total female cohort, respectively. In the earlier analysis, women with PDSA were older and had more severe OSA resulting in a positive association between PDSA and retinal arteriolar narrowing.

Several mechanisms may account for the nonlinear inverse association between OSA severity and narrower retinal arterioles in men. Physiologically, retinal blood flow is autoregulated. Retinal arterioles are dilated in response to hypoxia.[36] Once reoxygenation occurs, retinal arterioles are constricted due to elevated concentrations of endothelin-1 acting on ET_A receptors.[37,38] Endothelin-1 concentrations may be increased proportionally to OSA severity,[39] and have a dose-dependent effect on retinal arteriolar constrictions.[40] The effect of endothelin-1 may be modified by antihypertensive therapy in OSA. For example, use of β-blockers could reduce the secretion of endothelin-1 from endothelium,[41] and calcium channel blockers attenuate the effect of endothelin-1 on arteriolar constrictions.[42] Therefore, the blunting AHI association with smaller retinal arterioles in men may be explained by multi-antihypertensive medications with high-dose use for resistant hypertension in severe OSA. The sensitivity of ET_A receptors to endothelin-1 is much stronger in men than in women,[43] which may explain the observed sex difference in the association between OSA and retinal arteriolar narrowing. Additionally, an animal study suggested that the sensitivity to endothelin-1 may decline with age, especially in females.[44] On the other hand, men but not women with severe OSA have been reported with higher risk of cardiac remodeling such as congestive heart failure, which elevates pulmonary wedge pressure and may affect retinal venular widening.[23]

Systemic inflammation and hyperglycemia, which are related to severe OSA, may cause diabetic retinopathy.[3,13,45] However, men with severe OSA seemed to have lower risk of diabetic retinopathy. This finding could be explained partly by the hypothesis that among individuals with severe OSA, retinal arteriolar dilatation occurred less in men, which may prevent blood overflow to the retina, possibly lowering the risk of retinal microaneurysms presenting as capillary leak despite chronic inflammation status.[46] In addition, some data indicate more endothelial dysfunction in women with OSA compared to men,[47] possibly increasing the risk of retinal microaneurysms in women with OSA.

The strengths of our study include an objective classification of OSA, the ethnic diversity of the MESA sleep cohort, the availability of digitally acquired retinal data on a variety of specific retinal signs, and the availability of a wide range of data on other covariates. Additionally, we used a sex-specific approach to prevent obscuring important sex-specific relationships. Almost all of the women in the current study were postmenopausal, which may mitigate the effect of sex hormones on the associations of OSA with retinal signs.

There are several limitations of our study. Data on some potential confounders such as inflammatory markers were not available and, as a result, we were not able to adjust fully for degree of inflammation. Only 50.5% of MESA visit 5 participants contributed PSG data for this analysis, possibly leading to a selection bias, although the baseline profile of characteristics among those who contributed PSG data and those who did not were similar. Since PSG was only obtained at a single visit, our analysis was cross-sectional and could not address the temporal association between OSA and retinal microvascular signs. Finally, the present study performed many tests, and we are aware this could inflate overall type I error rate. Due to the exploratory nature of this research problem, we selected the minimal requirement of multiple comparison procedure to satisfy statistical rigor and used $P<0.025$ as the significance level for the overall test of OSA severity. However, in some comparisons, there were borderline significant results that need to be clarified in further large studies that have sufficient power to detect the statistical difference between groups.

Conclusions

In MESA, the prevalence of OSA differed by sex as did OSA severity. Similarly, the associations between OSA severity and retinal microvascular signs may differ by sex. Moderate/severe OSA was associated with retinal vascular calibers in men, but not in women. In contrast, severe OSA was associated with retinal microaneurysms in women but not men. Further studies are necessary to explain the mechanisms underlying these sex-specific associations. A longitudinal follow-up for both OSA status and retinal microvascular changes will help to clarify any temporal associations. Moreover, whether sex-specific effects of OSA manifest on the microvasculature in other sites, including arterioles, venules, and vasa vasorum, also deserves investigation.

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Disclosures

None.

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