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Original Article

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Obstructive sleep apnea, nocturnal hypoxemia, and retinal microvasculature: The Atherosclerosis Risk in Communities Study

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Abstract

Study Objectives: Retinal microvascular pathology (RMP) and obstructive sleep apnea (OSA) are both cardiovascular disease risk factors. Limited data exists on their interrelationship. We tested the hypotheses that OSA and nocturnal hypoxemia would be associated with RMP and vessel calibers.

Methods: We conducted a quasi-cross-sectional analysis of 1625 participants in the Atherosclerosis Risk in Communities Sleep Heart Health Study. Participants completed in-home polysomnography monitoring (1996–1998) and were categorized by OSA severity (apnea–hypopnea index: <5, 5–14.9, and ≥15) and proportion of total sleep time with oxygen saturation < 90% (T90). Retinal photography (1993–1995) was used to assess RMP and measure vascular diameters (central retinal arteriolar equivalent [CRAE] and central retinal venular equivalent [CRVE]). Logistic and linear models were adjusted for demographics, behaviors, and BMI.

Results: Of the participants, 19% had OSA (AHI > 15) and 4% had RMP. Severe OSA was not associated with RMP [OR (95% CI): 1.08 (0.49 to 2.38)] or CRAE in adjusted models. OSA severity showed a positive linear relationship with CRVE; adjusted mean CRVE for those with OSA was 195.8 μm compared to 193.2 μm for those without OSA (Ptrend = 0.03). T90 was strongly associated with CRVE, but not with RMP or CRAE. Adjusted mean CRVE for T90 ≥ 5% was 199.0 and 192.9 for T90 < 1% (*p*trend < 0.0001).

Conclusions: OSA and T90 were not associated with RMP or CRAE. However, both OSA and T90 ≥ 5% were associated with wider venules, which may be early and indicative changes of increased inflammation and future risk of stroke and CHD.

Key words: obstructive sleep apnea; nocturnal hypoxemia; retinopathy; retinal microvasculature; retinal calibers

Introduction

The eye offers noninvasive direct access to the microvasculature [1]. Retinal microvascular pathology (RMP) such as microaneurysms, focal arteriolar narrowing/venular widening, arteriovenous nicking, and soft/hard exudates [2, 3] can arise within the retinal microvasculature through several pathophysiologic pathways [4]. Changes in the retinal vessel diameters (narrow arterioles and wide venules) occur early in the pathogenesis of retinal vascular disease and are sensitive to endothelial dysfunction from inflammation, changes in blood flow associated with tissue hypoxia, and other physiologic changes. Inflammation has been more strongly linked to central retinal venular equivalent (CRVE) widening than to central retinal arteriolar equivalent (CRAE) narrowing [5]. In contrast, CRAE narrowing has been more closely associated with markers of atherosclerotic disease than venular caliber [6].

The retinal vessels share similar anatomical and physiological properties with coronary and cerebral microcirculation and have been suggested as important biomarkers to estimate vascular health [1, 7] and particularly stroke [8]. Numerous cardiovascular risk factors have been linked to the development of RMP and changes in retinal calibers, and these retinal changes are one of the most common complications of diabetes [9]. Both the presence and severity of changes in the retinal microvasculature have been associated with hyperglycemia [10], though the results of three population-based studies have shown RMP to be common in non-diabetics, as well [11]. Previous studies have also reported a strong association between RMP and hypertension [3, 12]. A study within a non-diabetic population estimated the prevalence of RMP in hypertensive individuals as 11% and in normotensive individuals as 6% [13]. Chronic inflammation may also have a role in the development of RMP [14]. Meta-analyses have reported

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associations of RMP [7], and specifically retinal diameters [1, 7], with CVD incidence. Furthermore, retinopathy is also a leading cause of blindness and can often be avoided with timely intervention [15]. Given the morbidity directly and indirectly associated with RMP and retinal microvascular changes, there is a need for deeper understanding of the possible risk factors to identify opportunities for intervention.

Obstructive sleep apnea (OSA), a relatively common and often undiagnosed sleep disorder, is characterized by an upper airway obstruction causing brief periods of partial or total cessation of airflow [16, 17]. OSA has also been linked to cardiovascular disease [18, 19] through several pathways including hypertension [18, 19] and diabetes/prediabetes [18–20]. OSA may increase cardiovascular risk by leading to oxidative stress and chronic inflammation due to the repetitive nature of hypoxemia and reoxygenation [18, 19]. Retinal vessel diameters are particularly sensitive to endothelial dysfunction due to the reduction in nitric oxide bioavailability within the vascular endothelium resulting from oxidative stress and intermittent hypoxia [21, 22]. Among patients with diabetes, OSA is considered to be a risk factor for diabetic retinopathy, which is the leading cause of blindness in adults worldwide [23]. Since hypertension, diabetes, hypoxia, and inflammation are known to be common pathways in the development of RMP, it is plausible that OSA is also associated with RMP and early changes to the retinal microvasculature.

Using data from a subset of Atherosclerosis Risk in Communities Study (ARIC) participants who took part in the Sleep Heart Health Study (SHHS), we explored the association between OSA, measured via polysomnography, and several measures of RMP (including focal arteriolar narrowing/venular widening). We hypothesized that more severe OSA would be associated with greater odds of RMP. Furthermore, we hypothesized that OSA severity would be associated with wider venular diameters as measured by CRVE and narrower arteriolar diameters as measured by CRAE, after adjustment for covariates. Given the pathophysiology, we hypothesized the direction of the association being that OSA leads to RMP. Analyses were repeated using the exposure proportion of total sleep time with oxygen saturation < 90% (T90), which is a novel marker of nocturnal hypoxemia. Due to the timing of relevant data available in ARIC (polysomnography 1996–1998, retinal photography 1993–1995) the analysis is quasi-cross-sectional and thus requires nuanced interpretation.

Materials and Methods

Study population

The ARIC study is a prospective cohort of 15 792 men and women from four US communities. Participants were between 45 and 64 years of age at baseline in 1987–1989, and were selected using population-based probability sampling [24]. Since the initial visit, numerous follow-up visits have occurred, including visit 3 (1993–1995) and visit 4 (1996–1998), which are the focus of this analysis. The SHHS recruited a subset of 1920 ARIC participants (from the suburban Minneapolis, MN and Washington County, MD study sites) during the fourth ARIC visit (1996–1998) [25]. These participants underwent an in-home, overnight polysomnography recording. Individuals with sleep apnea treated with continuous positive airway pressure (CPAP), home oxygen therapy, or tracheostomy were not eligible to participate in SHHS. Of the 1,920 ARIC-SHHS participants, we excluded those with missing retinopathy data ($n = 110$), missing apnea–hypopnea index (AHI) or nocturnal hypoxemia ($n = 182$), or missing covariates ($n = 3$). Our final analytic sample included 1625 participants. Institutional review boards at each study site approved the study and written informed consent was obtained from all participants.

Retinal microvasculature

On the third visit (1993–1995), retinal photography was performed by trained technicians according to standard procedures [26]. After 5 minutes of dark adaptation, a 45-degree-retinal photograph of a randomly selected eye was obtained. This photograph was centered on the region of the optic disc and the macula and was taken with an autofocus camera.

Trained graders masked to participant characteristics used a computer-assisted approach to measure the calibers of all arterioles and venules coursing through a specified area surrounding the optic disc [26]. Individual vessel measurements were combined into summary indices—the CRAE and the CRVE—which estimated the central retinal arteriolar and venular caliber of the eye after taking into account the branching patterns. These measurements are reliable, with intragrader and intergrader reliability coefficients of 0.69 and 0.74 for CRAE and 0.89 and 0.77 for CRVE, respectively [26].

Graders also examined the photographs for signs of RMP including microaneurysms, flame-shaped hemorrhages, blot hemorrhages, or soft exudates. The graders' retinal vascular measurements had high reproducibility [26, 27]. For analysis, retinopathy was coded as 1 or 0 (presence vs. absence of RMP, respectively).

Sleep assessment

Using a portable monitor (PS-2 System; Compumedics Limited, Abbotsford, VIC, Australia), overnight unattended in-home polysomnography was conducted using methods that have been previously described [28]. The AHI, which sums the number of apneas and hypopneas (events) per hour of sleep, was used to categorize the severity of OSA. Apnea was defined as an absence or near absence of airflow for at least 10 seconds (regardless of desaturation level). Hypopnea was defined as a 30% decrease in the amplitude of airflow for at least 10 seconds (with at least a 4% decrease in oxygen saturation). Participants were categorized according to AHI as follows: <5.0 events/h (normal), 5.0–14.9 events/h (mild), ≥15.0 events/h (moderate or severe) [20]. As a secondary exposure, we also evaluated the proportion of total sleep time with oxygen saturation < 90%, also known as T90. Importantly, T90 is reflective of both intermittent hypoxemia occurring secondary to OSA events and also persistent hypoxemia (e.g. from chronic obstructive pulmonary disease) [29]. We categorized T90 for analysis as < 1%, 1% to < 5%, ≥5%.

Assessment of covariates

The ARIC study protocols have been described previously [24]. Covariates and potential mediators were assessed at the fourth visit (1996–1998), unless otherwise noted. Information on smoking status, physical activity (visit 3), and educational attainment (visit 1) were self-reported. Trained technicians obtained height and weight measurements to calculate BMI. Certified phlebotomists collected a fasting blood sample which was used to measure plasma lipids (LDL-C, HDL-C, and triglycerides), and serum glucose concentrations. Participants were classified as having diabetes if they had a fasting blood glucose of ≥ 126 mg/dL, used glucose-lowering medication, or

self-reported a physician diagnosis of diabetes. Blood pressure (BP) was measured twice from a seated position using a random-zero sphygmomanometer and the mean of the two measurements was used for analysis. Participants were classified as having hypertension if their systolic BP was ≥ 140 mmHg, diastolic BP was ≥ 90 mmHg, or they self-reported use of antihypertensive medication.

Data analysis

Due to nonconcurrent measurement of polysomnography (visit 4: 1996–1998) and retinal photography (visit 3: 1993–1995), this study design is quasi-cross-sectional. Descriptive statistics were calculated and stratified by OSA severity. To assess the relationship between OSA severity and RMP we performed a series of progressively adjusted logistic regression models: model 1 included age and sex as covariates. Model 2 additionally adjusted for education, physical activity, smoking, and BMI. Model 3 further adjusted for hypertension, diabetes, prevalent CHD, plasma lipids, and eGFR. OSA was modeled as a categorical variable to estimate odds ratios (ORs) and 95% confidence intervals (CIs) with participants with a normal AHI as the reference. To calculate *p*-values for linear trend, we modeled the three OSA categories ordinally. Additionally, cross-product terms for age, sex, hypertension, and diabetes are assessed for statistical interaction.

Linear regression analyses were performed to assess the relationship between OSA severity and CRVE/CRAE, with similar modeling as noted above. All analyses were conducted using SAS Studio (Cary, NC).

Analyses of T90 followed the same strategy as did analyses of OSA. Data are available, with appropriate approvals, through the NHLBI BioLINCC repository (https://biolincc.nhlbi.nih.gov) or through ARIC Coordinating Center via a Data and Materials Distribution Agreement (https://sites.cscc.unc.edu/aric/distribution-agreements).

Results

ARIC SHHS participants were 51.7% female, on average 62.3 years of age, and had a mean BMI of 28.7 kg/m^2. Of the participants, 19.4% had moderate/severe OSA, 30.1% had mild OSA, and 50.5% were without OSA (Table 1). Those with moderate/severe OSA were more likely to be older, male, current or former smokers, have hypertension or diabetes, and have a higher BMI than those with mild or no OSA. RMP was detected in 54 participants (3.3% of the sample). The mean ± SD of CRVE and CRAE in the sample were 191.5 μm ± 15.8 μm and 158.9 μm ± 14.3 μm, respectively.

The relationship between OSA severity and RMP was null across all statistical models (Table 2). After adjustment for age

Table 1. Participant Characteristics by Obstructive Sleep Apnea Severity Category: The ARIC Study

Category	Apnea–hypopnea index			
	Normal	Mild	Moderate/severe	Overall
	<5 events/hr	5–14.9 events/hr	15 + events/hr	
N total (%)	821	489	315	1,625
Demographics				
Age, mean years ± SD	61.5 ± 5.6	62.9 ± 5.4	63.6 ± 5.6	62.3 ± 5.6
Female *n* (%)	64.6	43.4	31.1	51.7
Education, n (%)				
<HS graduate	9.0	13.5	12.7	11.1
HS graduate	47.5	45.4	46.0	46.6
Some college	43.5	41.1	41.3	42.3
Behavioral characteristics				
Smoking *n* (%)				
Current	14.4	7.0	7.9	10.9
Former	44.2	51.9	54.0	48.4
Never	41.4	41.1	38.1	40.7
Physical Activity (leisure index) ± SD	2.5 ± 0.5	2.4 ± 0.5	2.4 ± 0.5	2.5 ± 0.5
Physiologic characteristics				
BMI, kg/m^2 ± SD	27.1 ± 4.4	29.2 ± 4.7	32.0 ± 5.5	28.7 ± 5.1
Prevalent diabetes, *n* (%)	9.0	15.5	16.5	12.4
Prevalent hypertension, *n* (%)	34.2	44.8	48.9	40.3
C-Reactive protein level, mg/L*	2.1 (1.0, 4.7)	2.2 (1.0, 4.7)	2.6 (1.3, 5.9)	2.2 (1.1, 4.8)
HDL cholesterol, mg/dL ± SD	52.5 ± 17.2	47.7 ± 14.8	43.1 ± 13.2	49.2 ± 16.2
LDL cholesterol, mg/dL ± SD	120.1 ± 32.0	124.8 ± 33.5	125.0 ± 30.9	122.4 ± 32.4
Triglycerides, mg/dL ± SD	148.8 ± 86.3	150.4 ± 78.2	165.5 ± 144.5	152.5 ± 98.3
eGFR, mL/min/1.73 m^2 ± SD	90.2 ± 13.4	88.6 ± 14.1	88.4 ± 14.1	89.4 ± 13.8
Prevalent CHD, *n* (%)	5.5	5.3	8.3	6.0

and sex, participants with moderate/severe OSA were not more likely to have RMP than those without OSA (OR: 1.37 [95% CI: 0.66, 2.85]), though precision was poor. Findings were further attenuated after additional adjustment. There was no evidence that age, sex, diabetes, or hypertension modified the relationship between OSA severity and RMP (*p*-value for cross-product terms > 0.05).

In our linear regression models, greater OSA severity was associated with higher mean CRVE (Table 3). After accounting for age and sex (model 1), the mean CRVE in participants with moderate/severe OSA was 193.9 μm compared to 190.6 μm for those without OSA (*p*-value for linear trend = 0.0004). After additional adjustment for behaviors and BMI (model 2), the mean CRVE for those with severe OSA was 195.8 μm compared to 193.2 μm for those without OSA (*p*-value for linear trend = 0.03). Associations persisted with additional adjustment for potential mediators including relevant cardiovascular risk factors (model 3; *p*-value for linear trend = 0.02). In the unadjusted model, moderate/severe OSA was associated with narrower mean CRAE (*p*-value for linear trend 0.02); however, this association was null after adjustment for covariates (models 1–3).

Analyses were conducted examining T90 category as the exposure. Of the participants, 14.2% had a T90 ≥ 5%, 15.3% between 1 to ≤%, and 70.6% <1%. No significant associations were observed between T90 and RMP (Table 4) or CRAE, though associations were observed with CRVE (Table 5). After accounting for age and sex (model 1), the mean CRVE in participants with T90 ≥ 5% was 197,7 μm compared to 190.3 μm for those with T90 < 1% (*p*-value for linear trend < 0.0001). After additional adjustment for behaviors and BMI (model 2), the mean CRVE for those with T90 ≥ 5% was 199.0 μm compared to 192.9 μm for participants with T90 < 1% (*p*-value for linear trend < 0.0001). Associations persisted after adjustment for potential mediators (model 3; *p*-value for linear trend < 0.0001).

Discussion

In this community-based sample, we did not find an independent association between objectively measured OSA severity or T90, as assessed by in-home polysomnography, and retinopathy, as assessed by retinal photography. However, we did observe novel findings. Both greater OSA severity and T90 were associated with wider retinal venules, even after adjusting for traditional cardiovascular risk factors.

Table 2. Obstructive Sleep Apnea and Retinal Microvascular Signs: The ARIC Study

OSA severity	**Normal**	**Mild**	**Moderate/severe**	
Apnea–hypopnea index	**<5 events/hr**	**5–14.9 events/hr**	**15 + events/hr**	
Median AHI	1.77	8.53	24.60	
N total	821	489	315	
N microvascular abnormalities (%)	21 (2.6%)	20 (4.1%)	13 (4.1%)	
Retinal microvascular abnormalities [OR (95% CI)]				*p*-trend
Model 1	1 (Reference)	1.45 (0.77, 2.73)	1.37 (0.66, 2.85)	0.33
Model 2	1 (Reference)	1.34 (0.70, 2.58)	1.08 (0.49, 2.39)	0.75
Model 3	1 (Reference)	1.22 (0.61, 2.41)	1.00 (0.44, 2.28)	0.94

Model 1: Adjusted for age and sex
Model 2: Adjusted for M1 + education, physical activity, smoking, and BMI
Model 3: Adjusted for M2 + prevalent hypertension, diabetes, CHD, eGFR, LDL cholesterol, HDL cholesterol, and triglycerides.

Table 3. Adjusted Mean Central Retinal Arteriolar and Venular Equivalents According to Obstructive Sleep Apnea Category: The ARIC Study

OSA severity	**Normal**	**Mild**	**Moderate/severe**	
Apnea–hypopnea index	**<5 events/hr**	**5–14.9 events/hr**	**15 + events/hr**	
N total	773	457	287	
Central retinal arteriolar equivalent (CRAE) μm				*p*-trend
Crude mean (95% CI)	160.0 (159.0, 161.0)	*157.6 (156.3, 158.9)*	158.3 (156.6, 159.9)	0.02
Model 1 (95% CI)	159.7 (158.7, 160.7)	*157.7 (156.4, 159.1)*	158.7 (157.0, 160.3)	0.13
Model 2 (95% CI)	161.1 (159.8, 162.4)	159.6 (158.1, 161.1)	160.5 (158.6, 162.4)	0.36
Model 3 (95% CI)	160.9 (158.9, 162.8)	159.7 (157.5, 161.8)	160.8 (158.3, 163.2)	0.67
Central retinal venular equivalent (CRVE) μm				
Crude mean (95% CI)	190.1 (189.0, 191.3)	191.8 (190.3, 193.2)	*194.4 (192.6, 196.3)*	<0.0001
Model 1 (95% CI)	190.6 (189.4, 191.7)	191.7 (190.2, 193.1)	*193.9 (192.0, 195.7)*	0.004
Model 2 (95% CI)	193.2 (191.9, 194.6)	194.4 (192.8, 196.1)	*195.8 (193.8, 197.8)*	0.03
Model 3 (95% CI)	194.3 (192.2, 196.5)	195.4 (193.1, 197.8)	*197.0 (194.4, 199.7)*	0.02

Model 1: Adjusted for age and sex
Model 2: Adjusted for M1 + education, physical activity, smoking, and BMI
Model 3: Adjusted for M2 + prevalent hypertension, diabetes, CHD, eGFR, LDL cholesterol, HDL cholesterol, and triglycerides.
Italic: *p*-value is significant when comparing group to the normal group

Table 4. Proportion of Total Sleep Time < 90% Oxygen Saturation and Retinal Microvascular Signs: The ARIC Study

Nocturnal hypoxemia				
Proportion of total sleep time < 90% Oxygen saturation	**<1%**	**1%–<5%**	**≥5%**	
Median nocturnal hypoxic impact	0.03	2.26	10.47	
N total	1,147	248	230	
N microvascular abnormalities (%)	33 (2.9%)	8 (3.2%)	13 (5.7%)	
Retinal microvascular abnormalities [OR (95% CI)]				*p*-trend
Model 1	1 (Reference)	1.02 (0.46, 2.25)	1.77 (0.91, 3.45)	0.13
Model 2	1 (Reference)	0.91 (0.41, 2.05)	1.41 (0.68, 2.93)	0.43
Model 3	1 (Reference)	0.78 (0.33, 1.81)	1.13 (0.52, 2.46)	0.87

Model 1: Adjusted for age and sex
Model 2: Adjusted for M1 + education, physical activity, smoking, and BMI
Model 3: Adjusted for M2 + prevalent hypertension, diabetes, CHD, eGFR, LDL cholesterol, HDL cholesterol, and triglycerides.

Table 5. Adjusted Mean Central Retinal Arteriolar and Venular Equivalents According to Proportion of Total Sleep Time < 90% Oxygen Saturation: The ARIC Study

Nocturnal hypoxemia				
Proportion of total sleep time < 90% Oxygen saturation	**<1%**	**1%–<5%**	**≥5%**	
N total	1074	234	209	
Central retinal arteriolar equivalent (CRAE) μm				*p*-trend
Crude mean (95% CI)	158.9 (158.0, 159.7)	159.0 (157.2, 160.9)	159.2 (157.3, 161.2)	0.71
Model 1 (95% CI)	158.7 (157.8, 159.5)	159.3 (157.5, 161.2)	159.7 (157.7, 161.6)	0.30
Model 2 (95% CI)	160.2 (159.1, 161.3)	161.2 (159.3, 163.2)	161.4 (159.3, 163.5)	0.21
Model 3 (95% CI)	160.2 (158.3, 162.1)	161.3 (158.8, 163.8)	161.1 (158.6, 163.6)	0.30
Central retinal venular equivalent (CRVE) μm				
Crude mean (95% CI)	190.1 (189.2, 191.0)	192.0 (190.0, 194.0)	*197.9 (195.7, 200.0)*	<0.0001
Model 1 (95% CI)	190.3 (189.4, 191.2)	191.7 (189.7, 193.7)	*197.7 (195.6, 199.8)*	<0.0001
Model 2 (95% CI)	192.9 (191.7, 194.2)	194.2 (192.1, 196.3)	*199.0 (196.7, 201.3)*	<0.0001
Model 3 (95% CI)	193.9 (191.8, 195.9)	194.9 (192.2, 197.7)	*199.7 (196.9, 202.5)*	<0.0001

Model 1: Adjusted for age and sex
Model 2: Adjusted for M1 + education, physical activity, smoking, and BMI
Model 3: Adjusted for M2 + prevalent hypertension, diabetes, CHD, eGFR, LDL cholesterol, HDL cholesterol, and triglycerides.
Italic: *p*-value is significant when comparing group to the normal group.

Our findings connecting OSA severity and nocturnal hypoxemia with wider venules are potentially meaningful. Vessel diameters are sensitive to endothelial dysfunction from inflammation, blood flow changes due to hypoxia, and other physiologic changes [4]. Prior research has shown RMP, CRVE, and CRAE to all be associated with risk of incident CVD [1, 7], including in ARIC [30, 31], though associations have not always been consistent with some studies suggesting a greater role for CRVE than for CRAE [32, 33]. Emerging literature also suggests that T90 represents a more comprehensive measure of hypoxic burden than OSA, and may be a stronger marker of cardiovascular risk [29]. Taken together, our findings support connections between OSA and hypoxic burden with greater retinal venular diameters.

A prior SHHS paper evaluated the association between OSA and retinopathy using ARIC and Cardiovascular Health Study data and reported null findings [34]. Cardiovascular Health Study participants were not included in the present paper. For ARIC participants, the same polysomnography and retinal photographs were used in the prior paper and the present analysis. However, there are additional important methodological differences between the papers to note. In the prior paper, the authors only defined OSA according to respiratory disturbance index quartiles, with quartile four having a lower bound of 11.7 (below the clinical threshold for even moderate OSA), did not include a measure of hypoxic burden, and evaluated retinal venular and arteriolar diameters as a ratio, rather than separately [34]. Our analysis is unique as we used a more clinically meaningful OSA cutpoint (≥15 events/hour indicating moderate or severe disease), assessed associations with T90, and evaluated CRAE and CRVE indices separately. The association between OSA and most cardiovascular outcomes is nonlinear, with elevated disease often occurring only with moderate/severe OSA, thus motivating our analysis with the more rigorous cutpoints. Evaluating CRVE and CRAE separately is also an important contribution of the present analysis, since those metrics may be associated with different etiologic processes [5, 6] and some evidence suggests they have different associations with CVD [32, 33].

Despite AHI being the clinically accepted measure of OSA, there has been a recent push to move beyond measuring OSA impact solely by event frequency. While there is no consensus on what is the best measure of OSA beyond AHI, recent studies have connected measures of hypoxic burden duration and severity, including T90, to CVD risk [29]. Our findings connecting T90 with CRVE support the utility of examining hypoxic burden, in

addition to AHI, to better understand the risks associated with sleep-disordered breathing.

Limitations of the current study should be noted. First, a single 45-degree retinal photograph was used to identify abnormalities though the standard clinical practice uses multiple 45-degree fields [35]. As such, we may have underestimated the prevalence of retinopathy. Second, OSA was assessed using an in-home test rather than in a sleep laboratory. AHI measured by in-home polysomnography is highly concordant to laboratory polysomnography, [36] and is preferred to self-reported OSA. We selected AHI as our primary exposure given its widespread use in clinical settings. However, other metrics of sleep may also have value. In secondary analyses, we did explore T90, which is a novel measure of hypoxic burden and may provide a more comprehensive assessment of duration and severity of hypoxemia [29]. Third, precision was limited overall, and particularly when RMP was the outcome of interest. Therefore we were unable to conduct meaningful analyses stratified by the presence of diabetes mellitus, which is unfortunate given the growing understanding of OSA as a risk factor for diabetic retinopathy [23]. Related, no measurement of the duration of diabetes was considered. Fourth, the study design was quasi-cross-sectional since sleep assessment took place around visit 4 (1996–1998) while retinal photography was performed approximately 3 years prior (1993-1995), thus limiting causal inference.

In conclusion, this study found no associations between OSA severity or T90 and retinopathy or CRAE. However, participants with moderate/severe OSA or T90 ≥ 5% had wider venules, which may be early and indicative of changes of increased inflammation and future risk of CVD.

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Author Contributions

Nathan Hoeft (Writing—original draft [Equal]), Kelsie Full (Writing—review & editing [Equal]), Jeffrey Misialek (Formal analysis [Lead], Methodology [Equal], Writing—review & editing [Supporting]), Kamakshi Lakshminarayan (Writing—review & editing [Equal]), Srishti Shrestha (Writing—review & editing [Equal]), Jennifer Deal (Writing—review & editing [Equal]), and Pamela Lutsey (Writing—original draft [Equal]).

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