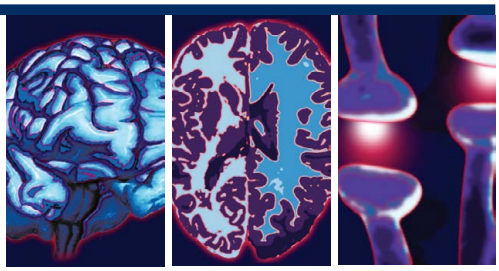
Review



Obstructive sleep apnea and retinal microvascular characteristics: a brief review

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ABSTRACT

Obstructive sleep apnea (OSA) causes intermittent nocturnal hypoxemia and is associated with obesity, diabetes, inflammation, endothelial dysfunction, and hypertension, possibly leading to micro- and macro-vascular disease. OSA has been associated with higher risk of clinical cardiovascular disease (CVD) independent of traditional risk factors and severity of atherosclerosis. Microvascular disease may be a potential mediator for the association of OSA with clinical CVD. However, evidence for the association between OSA and microvascular dysfunction is conflicting. Since the retinal microvasculature is structurally and functionally similar to microvasculature elsewhere in the body and can be directly visualized via ophthalmoscopy, several studies have assessed the relationship of OSA with retinal microvascular characteristics but shown inconsistent results. Notably, the multi-ethnic study of atherosclerosis (MESA) recently revealed that the associations of OSA severity with retinal microvascular signs may differ by sex. Moderate/severe OSA was associated with retinal vascular calibers in men, but not women. In contrast, severe OSA was associated with retinal microaneurysms in women but not men. To our knowledge, the clinical course of OSA differs by sex with women on average having less severe sleep apnea than men at younger ages, with differences narrowing after menopause. Whether these findings in MESA were related to sex differences in OSA exposure needs further study. Moreover, whether sex-specific effects of OSA manifest on the microvascularature in other sites, including arterioles, venules, and vasa vasorum, also deserves investigation.

Keywords

Cardiovascular disease, Obstructive sleep apnea, Retinal microvascular characteristics, Sex difference

Introduction

Obstructive sleep apnea (OSA) is a common syndrome with generalized effects on multiple systems in human body. OSA usually arises from airway closure at a supraglottic area when one sleep, causing absent or diminished airflow despite persistent respiratory effort, followed by hypoxia-induced arousal and termination of apnea [1]. Across the population, OSA is the major form of sleep apnea, affecting about 15 million American adults [2]. The prevalence of clinically relevant OSA in the general population

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increases with age [3] and is only 6% in women compared with 14% in men [4].

■ OSA as a vascular risk factor and possible mechanisms involved

In previous studies, OSA has been associated with a wide range of clinical cardiovascular disease (CVD) including coronary heart disease, ischemic stroke, heart failure, and atrial fibrillation [3], independent of traditional risk factors [5].

The nature of OSA is cycles of deoxygenation and reoxygenation triggering production of reactive oxygen species and thus increasing oxidative stress leading to endothelial damage [6]. OSA causes sleep arousals accompanied with sympathetic bursts and persisting increase of sympathetic drive [7,8], which would contribute to increased vascular risk [9]. OSA also causes systemic inflammation which is associated with progression of atherosclerosis [10]. Nuclear factor kappa B, one of critical inflammation mediator, is found with significantly higher activation in patients with OSA than controls [11]. Several inflammatory markers, e.g. cytokines, matrix metalloproteinases, and acute phase proteins, endothelial adhesion molecules, are also positively associated with OSA [12]. OSA is also associated with endothelial dysfunction. OSA was shown to be associated with increased expression of adhesion molecules on monocytes and increased adhesion of monocytes to endothelium, while adhesion molecules were downregulated by continuous positive airway pressure [13], a recommended treatment for OSA. Another study also showed lower endothelial repair capacity in OSA, by measuring circulating endothelial progenitor cell levels [14]. A recent study found endocan, a novel surrogate marker for endothelial damage, was significantly associated with severity in AHI and endothelial dysfunction of OSA [15]. OSA is also associated with poor control of diabetes and hypertension which may contribute additional risk for vascular damage [5,16,17].

■ Microvascular disease: a potential mediator between OSA and clinical CVD

Microvascular disease may be a potential mediator for the association between OSA and clinical CVD. However, current evidence for the association between OSA and microvascular disease is conflicting.

Since most previous studies approached the microvasculature in target organs indirectly by renal microalbuminuria measurements, cardiac perfusion scan, and cerebral imaging studies, the results may not be convinced in the absence of pathological approval. The retinal microvasculature is structurally and functionally similar to microvasculature elsewhere in the body and can be directly visualized via ophthalmoscopy [18]. Several studies have assessed the relationship of retinal microvascular signs with multiple CVD risk factors. Retinal arteriolar narrowing is strongly related to age and hypertension [19], while retinal venular widening is related to cigarette smoking, metabolic abnormalities, inflammation, and atherosclerosis [20,21]. Retinopathy signs, specifically microaneurysms, hemorrhages, and cotton wool spots found in patients with diabetes, are also prevalent in the general population (5-10%), and may be related to age, obesity, hyperglycemia, elevated blood pressure, and inflammation [21].

Because there lacks substantial evidence for the relationship of OSA with microvascular characteristics, we made a brief review of literatures regarding the topic where microvasculature were evaluated by indirect methods and direct fundus photography **(Table 1)**.

There were a number of studies regarding the relationship between OSA and microvascular dysfunction in kidney in the Asian and Caucasian populations with or without hypertension [22-29]. Renal microvascular disease was usually evaluated by single dipstick or 24-hour urinary analysis for microalbuminuria, proteinuria, albumin-to-creatinine ratio, and serum cystatin measurements. In general, intermittent hypoxemia marked by oxygen desaturation index (<3%) greater than 5 times per hour, minimal oxygenation, or duration of oxygen saturation <90% were consistently associated with renal microvascular injury [22,24-26,28,29]. In contrast, the results for the association of severity of OSA defined by apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) with renal microvascular injury were conflicting [22-24,27-29]. Some studies revealed that there was an association but some showed null association. In addition, the Osteoporotic Fractures in Men (MrOS) study and the study by Ting *et al.* demonstrated that older age may be a moderator for the AHI or RDI association [24-26,28].

Similarly, several studies regarding the relationship of OSA with cerebral and brain stem small vessel disease in the Asian and Caucasian subjects with or without cerebrovascular disease

Table 1: Obstructive Sleep Apnea and Microvascular Dysfunction in Kidney, Brain, and Heart.

Study	Subjects	OSA parameters	Microvascular Dysfunction Evaluation	Main Findings
OSA and kidney injury				
Zhang et al. 2016; Cross-sectional [29]	Chinese patients with diabetes (n=880)	AHI, average SPO_2, and the cumulative time of SPO_2 <90%	Microalbuminuria	*Nocturnal hypoxemia but not AHI were associated with microalbuminuria
Chen et al. 2015; Cross-sectional [27]	Chinese patients with hypertension and OSA (n=457)	Severe: AHI >30; control: AHI <10	24-hr urinary protein; and serum cystatin C	*OR: 4.9 (95% CI: 1.6-15.1) for 24-hr urinary protein; *OR: 6.1 (95% CI: 1.3-29.3) for serum cystatin C
Ting et al. 2015; Cross-sectional [28]	Chinese male subjects (n=300)	AHI and the cumulative time of SPO_2 <90%	Proteinuria at single dipstick urinalysis	*Nocturnal hypoxemia but not AHI was associated with proteinuria; *However in those age > 49 year, AHI >21 was associated with proteinuria
Bulcun et al. 2015; Cross-sectional [26]	Patients with OSA (n=98) and non-apneic snoring subjects (n=26)	OSA defined by AHI vs. non-OSA	Urinary albumin excretion (UACR)	*Minimal O_2 inversely and desaturation index positively associated with greater UACR
Furukawa et al. 2013; Cross-sectional [25]	Japanese patients with diabetes (n=513)	ODI >3% ≥5/hr vs. those <5/hr	Urinary albumin excretion (UACR)	*Nocturnal hypoxemia was associated with greater UACR (in overall cohort and in women, but not in men).
Canales et al. 2011; Cross-sectional [24]	Old male subjects ≥67 years in the MrOS study (n=507)	RDI and the cumulative time of SPO_2 <90%	Urinary albumin excretion (UACR)	*Nocturnal hypoxemia but not RDI was associated with greater UACR after adjusting for all covariates
Agrawal et al. 2009; Cross-Sectional [23]	Obese adults for bariatric surgery (n=91)	AHI	Urinary albumin excretion (UACR)	*Log AHI was not associated with UACR
Tsioufis et al. 2008; Cross-Sectional [22]	Untreated hypertensive patients with OSA (n=62) and those without OSA (n=70)	AHI and minimal O_2 saturation	Urinary albumin excretion (UACR)	*Minimal O_2 inversely and AHI positively associated with greater UACR
OSA and brain injury				
Kepplinger et al. 2014; Cross-sectional [38]	Patients with acute stroke (n=56)	Moderate to Severe: AHI ≥15; control: AHI <5	WMC and lacunar infarcts in brain MRI	Moderate/severe OSA was associated with cerebral WMC
Kim et al. 2013; Cross-Sectional [37]	Korean adult subjects free of CVD (n=503)	Moderate to Severe: AHI ≥15; control: AHI <5	WMC in brain MRI	Moderate/severe OSA was associated with cerebral WMC
Kiernan et al. 2011; Cross-Sectional [36]	Patients with hypertension and free of CVD (n=62)	Moderate to Severe: AHI ≥15; control: AHI <5	WMC in brain MRI	OSA was not associated with cerebral WMC
Nishibayashi et al. 2008; Cross-Sectional [35]	Japanese patients free of CVD (n=192)	Moderate to Severe: AHI ≥15; control: AHI <5	WMC and lacunar infarcts in brain MRI	Moderate/severe OSA had higher prevalence of cerebral WMC and lacunar infarcts
Eguchi et al. 2005; Cross-Sectional [33]	Japanese patients with high vascular risk (n=146)	ODI >3% using the frequency of ≥ and <5.6/hr	WMC and lacunar infarcts in brain MRI	Nocturnal hypoxemia was associated with cerebral WMC and lacunar infarcts
Robbins et al. 2005; Cross-Sectional [34]	Old adults free of CVD (n=843)	OSA defined by RDI	WMC in brain MRI	OSA was not associated with cerebral WMC
Ding et al. 2004;. Cross-Sectional [32]	Old adults free of cerebrovascular disease (n=789)	AHI and the arousal index	WMC in brain MRI	The arousal index was inversely associated with brainstem WMC but AHI was not.
Harbinson et al. 2003; Cross-Sectional [31]	Patients with acute stroke (n=78)	AHI and ODI	WMC in brain MRI	AHI was associated with cerebral WMC
Davies et al. 2001; Case Control [30]	Patients with more severe OSA (n=45) and those without OSA (n=45)	Moderate to severe OSA defined by AHI	WMC and lacunar infarcts in brain MRI	OSA was not associated with cerebral WMC
OSA and cardiac injury				
Butt et al. 2011; Case Control [41]	Patients with severe OSA; hypertensive patients; healthy controls (each n=36)	Moderate to severe OSA defined by AHI	MPI by contrast echocardiography	*Moderate/severe OSA was associated with myocardial perfusion impairment
Nakashima et al. 2011; Cross-Sectional [42]	Patients with STEMI following PCI (n=100)	OSA defined by AHI	MPI by Doppler coronary flow velocity reserve	*OSA may impair myocardial tissue perfusion following primary PCI.

Lee et al. 2009; Cross-Sectional [43]	Patients with STEMI following PCI (n=105)	OSA defined by AHI	MPI by ST segment resolution and myocardial blush grade	*OSA not associated with impaired microvascular perfusion after primary PCI.
Orea-Tejeda et al. 2003; Case studies [40]	Morbid obese patients with OSA (n=14)	OSA defined by AHI	MPI by SPECT with technetium-labeled sestamibi	*Myocardial perfusion defects appear to occur with highest frequency and severity at nighttime sleep

AHI, apnea-hypopnea index (times/hour); MPI, myocardial perfusion imaging; MRI, magnetic resonance imaging; MrOS, the Osteoporotic Fractures in Men study; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention; RDI, respiratory disturbance index; SPECT, single photon emission computed tomography; STEMI, ST segment elevation myocardial infarction; UACR, urinary albumin-to-creatinine ratio; WMC, white matter change

were performed [30-38]. Cerebral small vessel disease was represented by white matter changes or lacunar infarcts in brain magnetic resonance imaging (MRI) or computed tomography studies. There were no consistent results for a positive relationship between moderate to severe OSA classified by AHI or RDI and cerebral small vessel disease [30-38]. The results were also uncertain for the association of intermittent hypoxemia with cerebral small vessel disease [31]. In addition, one study by Ding *et al.* showed that the arousal index might be inversely associated with brain stem white matter changes in MRI [32].

With regard to the association between OSA and cardiac microvascular dysfunction, some reports were conducted in the Asian and Caucasian patients with or without acute myocardial infarction [39-42]. Microvascular dysfunction was evaluated by myocardial perfusion imaging: contrast echocardiography, Doppler coronary flow velocity reserve, or single photon emission computed tomography. The results regarding the association between moderate to severe OSA defined by AHI and myocardial microvascular dysfunction in patients with acute myocardial infarction following primary percutaneous coronary intervention were controversy as well [42,43]. This finding might be confounded by the production of lipid microemboli from atheroma plaque rupture [44]. In addition, one case series by Orea-Tejeda *et al.* showed that myocardial perfusion defects appear to occur with highest frequency and severity during nighttime sleep rather than daytime awake [40] **(Table 2)**.

Through the ocular fundus, retinal blood vessels can be visualized easily and noninvasively. Retinal vessels, which share similar embryological origin, anatomical features and physiological characteristics with cerebral and coronary vasculatures, provide an opportunity to view microvascular abnormalities and reflect the status of CVD [45-47].

As above review, there is emerging evidence showing that OSA is a risk factor of CVD. Moreover, hypoxia and elevated sympathetic tone resulted from OSA can lead to vascular endothelium dysfunction and abnormal autoregulation. Therefore studies were designed to investigate the relationship between OSA and retinal microvascular changes. Boland *et al.* first used arteriolar-to-venular ratio (AVR) to quantitatively prescribe retinal arteriolar narrowing, and found an increase in respiratory disturbance index (RDI) from 0 to 10 was associated with a decrease of AVR [48]. The overall prevalence of retinal microvascular abnormalities, including microaneurysms, hemorrhages, soft or hard exudates, macular edema, intraretinal microvascular abnormalities, venous beading, new vessels at the disc or elsewhere, vitreous hemorrhage, disc swelling, or laser photocoagulation scars, was 6.6%. Except microaneurysms, the prevalence of which was doubled in the upper 2 versus the lower 2 RDI quartiles, further multivariable analysis showed that there was no clear association between other retinal microvascular abnormalities and the severity of OSA (i.e. RDI or hypoxemia) [48].

A low retinal AVR may be contributed from smaller retinal arteriolar caliber or a larger retinal venular diameter. Smaller retinal arteriolar diameters were related to increasing blood pressure [49,50], and were not associated with the markers of atherosclerosis except increased carotid intima–media thickness [49]. Larger venular diameters were associated with several markers of atherosclerosis [49], inflammation [49,50] and dyslipidemia [49-51]. With regard to different pathogenesis in the changes of retinal arterioles and venules, Shankar *et al.* investigated the association between OSA and retinal arteriolar and venular diameters separately [52]. Higher AHI was positively associated with retinal venular widening but not with arteriolar narrowing, and was independent of age, sex, body mass index, diabetes, and serum lipid levels [52]. These findings suggest that the microvascular dysfunction of OSA might be related to atherosclerosis inflammation, and factors that are associated with widening of retinal venules.

Table 2: OSA and Retinal Microvascular Characteristics.

Study	Subjects	OSA parameters	Microvascular Dysfunction Evaluation	Main Findings
OSA and retinal microvascular signs in the general population				
Boland et al. 2004; Cross-sectional [48]	The SHHS cohort (n= 2,927)	SDB severity defined by RDI	Retinal AVR and specific retinopathy	*RDI was inversely correlated with retinal AVR only when RDI <10; *Prevalence of microaneurysms in the upper 2 versus the lower 2 RDI quartiles doubled; *No analysis for sex difference
Shankar et al. 2013; Cross-sectional [52]	The WSCS cohort (n=476)	SDB severity defined by AHI	Retinal arteriolar narrowing (diameter in the narrowest quartile), retinal venular widening (the widest quartile)	*Higher AHI was associated retinal venular widening; *No analysis for sex difference
OSA and retinopathy in patients with diabetes				
Kosseifi et al. 2010; Cross-sectional [65]	Patients with well-controlled type 2 diabetes. (n=98)	AHI and ODI	Retinopathy	*AHI and ODI were associated with retinopathy.
West et al. 2010; Cross-sectional [66]	Male patients with type 2 diabetes (n=240)	AHI and ODI	Retinopathy score; maculopathy score; microaneurysm score of English National Screening Programme	*Higher retinopathy, maculopathy and microaneurysm scores in the OSA group.
Rudrappa et al. 2012; Cross-sectional [67]	Obese male patients with type 2 diabetes. HbA1c: 7.0 –12.0% (n=31)	OSA (AHI >5, 15–29.9 and ≥30) vs. non-OSA	Retinopathy score; maculopathy score of National diabetic eye screening programme	*Higher retinopathy score and higher incidence of proliferative diabetic retinopathy in patients with OSA. *The severity of OSA (AHI) did not predict retinopathy score.
Banerjee et al. 2013; Cross-sectional [68]	Severe obese patients with type 2 diabetes HbA1c: 6.8-9.2%. (n=93)	OSA (AHI≥15); non-OSA (AHI<15), mean and minimum SpO_2, and duration of SpO_2 <90%	Diabetic retinopathy and maculopathy.	*Minimum SpO_2 was the only independent factor related to diabetic maculopathy. *There was trend of more maculopathy in patients with OSA than without OSA, but no significant difference.
Nishimura et al. 2015; Cross-sectional [69]	Patients with Type 2 diabetes	AHI, minimum SpO_2, duration of SpO_2 <90%, and ODI	Diabetic retinopathy	Minimum SpO_2 was associated with retinopathy.

AHI, apnea-hypopnea index (events/hour); BMI, body mass index; CAD, coronary artery disease; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; RDI, respiratory disturbance index (events/hour); SDB, sleep disordered breathing; SHHS, the Sleep Heart Health Study; WSCS, the Wisconsin Sleep Cohort Study

OSA is highly associated with diabetes mellitus which in turn contributes to retinopathy. OSA is associated with an increased prevalence of metabolic syndrome and type 2 diabetes [53-57], and 40% to 80% of patients with type 2 diabetes have OSA [58-60]. Current evidence suggest that hypoxia and inflammatory process leading to endothelial dysfunction play a pivotal role in the cardiovascular pathophysiology of OSA [61-64], which may also increase the development and progression of complications related to diabetes [65-69]. Diabetic patients with OSA were at higher risk of developing diabetic retinopathy and maculopathy than those without OSA [65-67]. The incidence of proliferative diabetic retinopathy was higher in diabetes with OSA [67]. However, AHI level did not predict the severity of diabetic retinopathy or maculopathy [67]. Minimal oxygen saturation during sleep is an independent predictive factor of the presence of diabetic retinopathy, especially maculopathy [68,69], suggesting that it was the severity of hypoxemia during sleep that correlated to the development of retinopathy **(Table 3)**.

The nature course of OSA differs between men and women. Men are more prone to be affected by OSA than women. Clinical manifestations of OSA also differ by sex, for example apnea/hypopnea are more severe among men with OSA, while snoring and daytime sleepiness seems similarly frequent between men and women [70,71]. Sex differences in sleep architecture are found both in OSA patients and the unaffected controls [72]. Fat distribution, upper airway anatomy, arousal response and sex hormones are possible factors for the sex differences in OSA [72].

Recently, the sex-specific association between OSA and retinal microvascular characteristics

Table 3: Sex differences in the Association of OSA With Retinal Microvascular Characteristics and Clinical CVD.

Study	Subjects	OSA parameters	Microvascular Dysfunction Evaluation	Main Findings
Retinal microvascular characteristics				
Furukawa et al. 2013; Cross-sectional [25]	The Japanese patients with diabetes (n=513)	ODI (>3%) ≥5/hr vs. those <5/hr	Retinopathy	*The ODI severity was not associated with retinopathy in both men and women.
Chew et al. 2016; Cross-sectional [73]	The MESA visit 2 sleep cohort (n=5803)	OSA defined by self-reported PDSA	Retinal vascular caliber and retinopathy	*In women, but not in men, PDSA was associated with retinal arteriolar narrowing. *PDSA was not associated with retinopathy
Lin et al. 2016; Cross-sectional [74]	The MESA visit 5 sleep cohort (n=1808)	OSA defined by AHI (severe: ≥30; moderate: 15-29.9; mild: 5-14.9; normal: <5)	Retinal arteriolar narrowing (diameter in the narrowest quartile), retinal venular widening (diameter in the widest quartile), and specific retinopathy	*Moderate/severe OSA was associated with retinal arteriolar narrowing and retinal venular widening in men, but not in women. *Severe OSA was associated with retinal microaneurysms in women, but not in men.
Coronary heart disease				
Gottlieb et al. 2010; Longitudinal [77]	The SHHS cohort (n= 4,422)	OSA defined by AHI >5	Incident coronary heart disease	*In men under 70 years old, OSA predicted incident coronary heart disease (HR: 1.10, 95% CI: 1.00- 1.21 per 10-unit increase in AHI) but not in older men or in women of any age.
Loke et al. 2012; Meta-analysis [78]	6 studies (n=8,785)	NA	Ischemic heart disease	*OSA is significantly associated with ischemic heart disease in men (OR, 1.92; 95% CI, 1.06–3.48), not in a female-specific study (OR: 0.4, 95% CI: 0.12–1.30)
Medeiros et al. 2016; Cross-sectional [81]	Middle-aged women (n=214)	AHI (moderate to severe: AHI>15; control: AHI <5)	Computed tomographic examination for CAC	Moderate to severe OSA is associated with the presence of CAC, in menopausal women (unadjusted, OR: 6.25, 95 % CI: 1.66–23.52; adjusted OR: 8.19, 95% CI: 1.66–40.3)
Stroke				
Redline et al. 2010; Longitudinal [76]	The SHHS cohort (n= 5,422)	OSA defined by AHI>5	Incident stroke	*OSA was associated with incident stroke in men.
Loke et al. 2012; Meta-analysis [78]	5 studies (n=8,435)	NA	Incident stroke	*OSA was associated with stroke in men (OR: 2.24, 95% CI: 1.57–3.19). *Higher AHI was associated with cerebrovascular events (OR per 10 units increase in AHI: 1.36, 95% CI: 1.26–1.43) in men
Heart failure				
Gottlieb et al. 2010; Longitudinal [77]	The SHHS cohort (n= 4,422)	OSA defined by AHI >5	Incident heart failure	*OSA predicted incident heart failure in men but not in women (HR per 10-unit increase in AHI: 1.13 [95% CI: 1.02 -1.26]).
Roca et al. 2015; Longitudinal [80]	The ARIC-SHHS cohort (n=1,645)	OSA (severe: AHI ≥30; moderate: 15-29.9; mild: 5-14.9; control: AHI <5)	Measurement of hs-TnT (risk factor of heart failure), incident heart failure and mortality	*OSA was associated with hs-TnT in women but not in men and associated with incident heart failure or death in the similarly pattern

AHI, apnea-hypopnea index (events/hour); ARIC, Atherosclerosis Risk in Community; AVR, arteriolar-venular ratio; CAC, coronary artery calcium; CI, confidence interval; hs-TnT, high-sensitivity troponin; HR, hazard ratio; MESA, the multi-ethnic study of atherosclerosis; NA: not available; ODI, oxygen desaturation index; OR, odds ratio; OSA, obstructive sleep apnea; PDSA, physician-diagnosed sleep apnea; RDI, respiratory disturbance index; SHHS, the Sleep Heart Health Study; UACR, urinary albumin-to-creatinine ratio

has been investigated in two cohorts at the multiethnic study of atherosclerosis (MESA) visits 2 and 5 respectively. Chew *et al.* [73] revealed that self-reported physician-diagnosed sleep apnea (PDSA) obtained from a sleep questionnaire was associated with retinal arteriolar narrowing in women (regression coefficient [β] −5.76; 95 % confidence interval (CI): −8.51- −3.02) but not in men and there was no association between PDSA and specific retinopathies at MESA visit 2. In contrast, Lin *et al.* [74], showed that moderate/severe OSA diagnosed by an objective polysomnography was associated with retinal arteriolar narrowing and venular widening in men (Odds ratio (OR): 1.65, 95% CI: 1.00-2.71 and OR: 1.80, 95% CI: 1.07-3.04, respectively) but not in women (OR: 1.10, 95% CI: 0.67-1.81 and OR: 0.91, 95% CI: 0.58-1.43). They also found severe OSA was associated with retinal microaneurysm, in women (OR: 3.22, 95% CI: 1.16-8.97) but not in men (OR: 0.59, 95% CI: 0.27-1.30) in an older cohort at MESA visit 5. These contradictory results might be attributed to different diagnostic tools and measurements of OSA. Although PDSA represented more severe OSA [75], the result of the PDSA association might be erroneous for the contamination of mild OSA in the unaffected individuals.

Similarly, although several studies have shown the association between OSA and clinical CVD, there were potential moderators such as sex to confound the relationship. In the sleep heart health study, there was a significant association between OSA and ischemic stroke in men, but not in women [76]. In another longitudinal study, Gottlieb *et al.* uncovered that OSA was significantly associated with incident coronary heart disease in men younger than 70 years of age (hazard ratio (HR): 1.10, 95% CI: 1.00-1.21, per 10-unit increase in AHI) but not in older men or in women of any age [77]. The study also found a significant association between OSA and incident heart failure in men but not in women (HR: 1.13, 95% CI: 1.02-1.26, per 10-unit increase in AHI).

A meta-analysis of several prospective studies showed that OSA is associated with stroke in men (OR: 2.24, 95% CI: 1.57-3.19) and an increase of 10 units in AHI is associated with a greater odds of cerebrovascular events (OR: 1.36, 95% CI: 1.26-1.43) [77]. The meta-analysis pointed that OSA was significantly associated with ischemic heart disease in studies predominately comprised of male participants (OR: 1.92, 95% CI: 1.06-3.48), but not in a female-specific study (OR: 0.4, 95% CI: 0.12-1.30). Without considering sex difference, the link between OSA and ischemic heart disease was not significant. Although the heterogeneity of included male-predominant studies was remarkable (I^2=70%). In brief, existing evidence may support OSA as a strong risk factor of cardiovascular and cerebrovascular diseases in men, while not in women, partially explained by small female samples [78]. A recent controlled trial also showed men have lower ejection fraction and more implanted stents than women in patients with OSA and acute coronary syndrome [79]. Roca *et al.* reported OSA was associated with high-sensitivity troponin T, a powerful risk factor of heart failure, in women but not in men (p=0.03 vs. p=0.94) and with incident heart failure or death in the similar pattern (women vs. men, p=0.01 vs p=0.1) [80]. Another study found that moderate to severe OSA was associated with the presence of coronary artery calcium, an indicator of atherosclerosis or coronary artery disease, in perimenopausal or menopausal women (OR: 8.19, 95%CI: 1.66-40.32) [81]. Sex hormones may play a role in male-to-female differences. In summary, men with OSA were likely to have greater risk of stroke and ischemic heart disease than those without OSA and this is consistent with the finding in animal study that the oxidative stress induced by intermittent hypoxia affected less vascular injury in females than males [82-84]. However, the sex difference in heart failure risk in OSA patients was inconsistent between studies.

Conclusion

In our brief review, there were substantial evidence for the relationship between nocturnal hypoxemia and renal microvascular injury, but the association of OSA severity defined by AHI with microvascular disease in target organs, i.e. kidney, heart, brain and retina is controversial. Sex may moderate the OSA association with microvascular dysfunction in each site and mediate the OSA effect on clinical CVD. Further studies are needed to investigate not only cross-sectional but also temporal association of OSA evaluated by AHI and the hypoxemia index with multiple microvascular characteristics and clinical CVD in men and women.

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