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ORIGINAL COMMUNICATION

Obstructive sleep apnea and cerebral white matter change: a systematic review and meta-analysis

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Abstract

Obstructive sleep apnea (OSA) can cause sleep fragmentation and intermittent hypoxemia, which are linked to oxidative stress. White matter changes (WMCs) representing cerebrovascular burden and are at risk factor for oxidative ischemic injury. The current study explores the mutual relationships between OSA and WMCs. We performed a systematic review of electronic databases for clinical studies investigating OSA and WMCs. Random-effects models were used for pooled estimates calculation. A total of 22 studies were included in the meta-analysis. The results revealed a significantly higher prevalence rate of WMCs [odds ratio (OR) 2.06, 95% confidence interval (CI) 1.52–2.80, $p < 0.001$] and significantly higher severity of WMCs (Hedges' $g = 0.23$, 95% CI 0.06–0.40, $p = 0.009$) in the patients with OSA than in controls. Furthermore, the results revealed a significantly higher apnea–hypopnea index (Hedges' $g = 0.54$, 95% CI 0.31–0.78, $p < 0.001$) and significantly higher prevalence rate of moderate-to-severe OSA (OR 2.86, 95% CI 1.44–5.66, $p = 0.003$) in the patients with WMCs than in controls, however there was no significant difference in the prevalence rate of mild OSA between the patients with WMCs and controls (OR 0.71, 95% CI 0.20–2.54, $p = 0.603$). OSA was associated with a higher prevalence and more severe WMCs, and the patients with WMCs had an increased association with moderate-to-severe OSA. Future large-scale randomized controlled trials with a longitudinal design are essential to further evaluate treatment in patients with OSA.

Keywords Sleep apnea · White matter change · Leukoaraiosis · Magnetic resonance imaging · Neuroimage · Meta-analysis

Introduction

Increasing evidence has demonstrated that obstructive sleep apnea (OSA) is significantly associated with the risk of cardiovascular diseases [1]. In the past decades, increasing clinical attention has focused on the impacts of OSA-related morbidity and mortality on systemic vascular consequences including hypertension, heart failure,

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coronary artery disease and stroke. Several models have been proposed for the pathophysiological mechanisms of OSA-related vascular disorders. Recurrent oxidative stress and chronic inflammation secondary to intermittent hypoxemia can impair neuronal synaptic function and cerebral perfusion [2]. In addition, endothelial dysfunction in patients with OSA may also debilitate endothelial-mediated vasodilation resulting in a reduction in the availability of nitric oxide and thereby promoting subsequent atherosclerotic changes [3, 4].

Cerebral white matter changes (WMCs) are traditionally defined as hyperintense lesions in the subcortical or periventricular areas on T2-weighted magnetic resonance imaging (MRI) or fluid attenuated inversion recovery (FLAIR) sequences. The presence of WMCs has been linked to the aging process and an increased risk of stroke, dementia and psychotic disorders [5, 6]. As a marker of cerebral small vessel disease, WMCs may present as subclinical brain infarcts, focal neurological symptoms or even global dysfunction. In spite of their considerable prevalence, the pathogenesis of WMCs and their association with traditional vascular risk factors remain largely unrecognized [7]. Moreover, WMCs have been histopathologically correlated with axonal loss, focal myelinolysis, reactive astrocytosis and vessel wall hyalinosis, suggesting that chronic hypoperfusion may aggravate WMCs [5].

The results of research on WMCs in OSA have been inconsistent. For example, patients with moderate-to-severe OSA have been reported to have a higher prevalence of silent cerebrovascular lesions [8], and a population-based study also found that moderate-to-severe OSA was an independent risk factor for developing WMCs in the elderly [9]. However, two earlier studies failed to demonstrate any significant association between OSA and WMCs [10, 11].

The disparity in the current results of correlation studies on OSA and white matter may be influenced by the different imaging modalities used to assess the extent of cerebral WMCs. Advanced MRI techniques such as diffusion tensor imaging (DTI) are increasingly being used as they can provide information about the quantitative parameters related to myelin or axonal changes. To explore white matter pathology in OSA, DTI sequences have broadened the clinical emphasis of brain microstructural alterations beyond the extent of cerebral small vessel disease and white matter fiber integrity [12, 13].

Previous neuroimaging studies have documented brain structural abnormalities in patients with OSA including reductions in focal gray matter and the presence of WMCs [9, 14, 15]. However, whether a contextual association exists between the disease severity of OSA and the degree of WMCs has not been well evaluated. To address the clinical significance of brain microstructural pathology in OSA, we conducted this systemic review of relevant clinical studies and performed a meta-analysis to determine the bidirectional relationship between OSA and WMCs.

Methods

We followed the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [16] in the current research. This meta-analysis fulfilled the requirements of the Institutional Review Board of Tri-Service General Hospital (TSGHIRB: B-105-12).

Search strategy

Two well-trained independent authors (BL Ho, PT Tseng) conducted the electronic searches of PubMed, EMBASE, ProQuest, ScienceDirect, Cochrane Library, ClinicalKey, Web of Science, and ClinicalTrials.gov with the keywords "sleep apnea or obstructive sleep apnea" and "white matter or leukoaraiosis" up to March 1, 2018. Furthermore, we performed manual searches of the reference lists of the eligible articles and other articles related to the current topic to increase the number of potential eligible articles [1, 2, 4–7].

The two authors initially screened the titles and abstracts for eligibility and made a temporary list of potentially eligible studies through consensus. The two authors then performed full-text examinations and resolved any inconsistencies with the consensus of a third reviewer (CY Hsu).

Inclusion and exclusion criteria

The inclusion criteria were: (1) formal published articles investigating comorbidities in patients with WMCs and OSA, either in terms of the presence of WMCs or statistical values representing the severity of WMCs, and (2) articles that were observed clinical trials in humans. We did not set any limitations to allow for the inclusion of as many potentially eligible articles as possible. The exclusion criteria were: (1) animal studies, and (2) trials not comparing comorbidities between WMCs and OSA, such as blood flow or metabolite rate in the brain.

Risk of bias assessment

We used the modified version of the Newcastle–Ottawa Scale (NOS) to assess the quality of the included studies (higher scores indicating better quality) [17]. Publication bias was appraised using funnel plots.

Data extraction

The primary outcomes were: (1) the prevalence rate of WMCs; (2) severity of WMCs in patients with or without

OSA; (3) the difference in apnea–hypopnea index (AHI), or (4) the prevalence rate of OSA in patients with or without WMCs. WMCs were defined as hyperintense lesions in the subcortical or periventricular areas on T2-weighted or FLAIR sequences, or neuronal changes on more advanced diffusion-weighted imaging (DWI). AHI was defined as apnea or hypopnea during sleep as per the American Academy of Sleep Medicine (AASM) guidelines. OSA was diagnosed by overnight polysomnography, nocturnal respiratory polygraphy [18] or a diagnostic sleep questionnaire [19–21].

Two independent authors (BL Ho, PT Tseng) extracted data from the eligible studies into a database according to a list of pre-determined variables of interest. The variables extracted included mean age (years), gender, body mass index (BMI), AHI, prevalence rate of systemic diseases (such as hypertension and diabetes mellitus (DM)), ethnicity (Caucasian, African American), education, and modified NOS scores. When data were missing in the articles, we tried to electronically contact the corresponding authors to request additional data.

Statistical analysis

Under the hypothesis of potential heterogeneity among the recruited articles, we used random-effects meta-analysis models rather than fixed-effects models [22] to analyze the data using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ, USA). We set the effect sizes (ESs) of the primary outcomes to be Hedges' g and 95% confidence intervals (CIs) to examine the statistical values representing the severity of WMCs in patients with OSA and controls and AHI in patients with WMCs and controls. Furthermore, we calculated the ESs with differences in means and 95% CIs for the differences in mean AHI between the patients with WMCs and controls. In addition, we set the ESs of the primary outcomes to be odds ratios (ORs) and 95% CIs to examine the comorbid rates of WMCs in the patients with or without OSA and the comorbid rates of OSA, either as mild or moderate-to-severe, in the patients with or without WMCs. Two-tailed p values of less than 0.05 were considered to be statistically significant.

We tested sensitivity with one study removed to evaluate whether the results of the meta-analysis were caused by any outliers within the recruited studies [23]. The Cochrane Q statistic with corresponding p value was used to evaluate potential heterogeneity [24]. We also used the I^2 statistic to indicate the proportion of heterogeneity among a study [25]. Visual inspection of funnel plots [26] and Egger's regression tests [27] were used to evaluate potential publication bias. In situations of significant publication bias, we used Duval and Tweedie's trim and fill test to adjust the ESs [28].

With the potential of heterogeneity and confounding effects, we performed meta-regression and subgroup meta-analyses to detect potential confounding factors. Specifically, when there were at least five datasets we performed meta-regression using the unrestricted maximum likelihood method. The variables of interest for meta-regression were mean age, gender distribution in the form of the proportion of females, BMI, AHI, prevalence rates of hypertension and DM, ethnicity (Caucasian, Africa American), and education. We also performed subgroup meta-analysis for WMCs as well as fiber integrity among the recruited studies. All of the meta- and subgroup meta-analyses were performed when there were at least three datasets [29].

Results

The flowchart of the current meta-analysis is shown in Fig. 1. A total of 75 articles were entered into the full-text screening stage, of which 53 were excluded because they did not meet the inclusion criteria (supplementary table 1). The remaining 22 articles were eligible for the current meta-analysis (Table 1) [9–13, 18–21, 30–42].

Methodological quality of included studies

Across the 22 studies, the average modified NOS score was 6.7 with a standard deviation (SD) of 2.8 (supplementary table 2).

The sensitivity test via one study removed revealed that the main results of the meta-analysis did not change after removing any one of the recruited studies. That is, the significance was not attributable to only one study.

Meta-analysis investigating the prevalence rate of WMCs in patients with OSA and controls without OSA

Among the ten eligible articles comparing the prevalence rate of WMCs in patients with OSA and controls without OSA [10, 19, 20, 30, 31, 33, 37, 38, 40, 42], the meta-analysis results revealed a significantly higher prevalence rate of WMCs in the patients with OSA compared to the controls without OSA ($k = 13$, OR 2.06, 95% CI 1.52–2.80, $p < 0.001$) (Fig. 2a) with significant heterogeneity (Q value = 23.28, $df = 12$, $p = 0.025$; $I^2 = 48.5\%$) but no publication bias via Egger's regression test (t value = 0.338, $df = 11$, $p = 0.742$).

The meta-regression procedure showed no significant associations between the prevalence rate of WMCs and other clinical variables including mean age ($p = 0.413$), female proportion ($p = 0.066$), BMI ($p = 0.935$), prevalence rate of hypertension ($p = 0.404$), or prevalence rate of DM ($p = 0.104$).

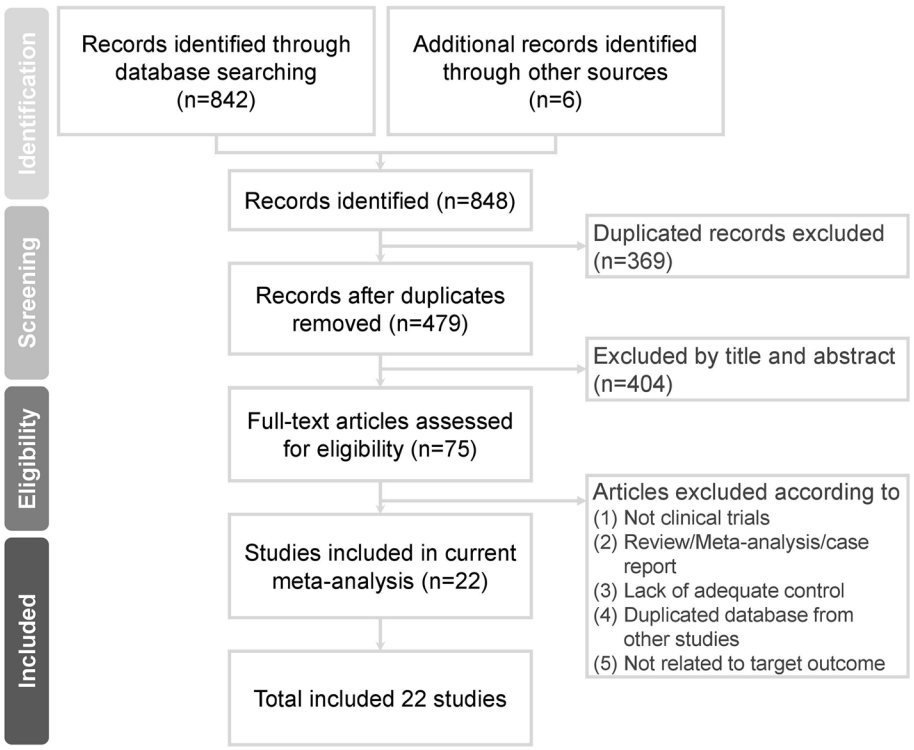


Fig. 1 Flowchart of the selection strategy for the current meta-analysis

Table 1 Characteristics of recruited studies

Study	Diagnosis	Group	Subject	Image targets	Sleep tools	Index of OSA	Mean age	Female (%)	Country
Davies et al. [10]	OSA	OSA (+)	45	WMH	PSG	> 4% falls in arterial SaO_2/hour	51.7 ± 10.4	0.0	UK
		OSA (−)	45				52.2 ± 10.4	0.0	
Macey et al. [12]	OSA	OSA (+)	41	Fiber integrity	PSG	AHI ≥ 15	46.3 ± 8.9	17.1	USA
		OSA (−)	69				47.5 ± 8.9	36.2	
Kiernan et al. [11]	WMC	ARWMC 9+	13	WMH	PSG	AHI ≥ 5	72.0 ± 7.0	31.0	USA
		ARWMC 5–8	18				69.0 ± 12.0	28.0	
		ARWMC 0–4	31				64.0 ± 13.0	35.0	
Schulz et al. [41]	OSA	ODI Q4	45	WMH	PSG	ODI > 7.5	57.9 ± 7.6	11.1	UK
		ODI Q3	46				59.7 ± 7.1	15.2	
		ODI Q2	44				57.5 ± 7.6	15.9	
		ODI Q1	48				55.8 ± 6.8	16.7	
Kim et al. [9]	WMC	WMC ≥ 5	39	WMH	PSG	AHI ≥ 5	67.1 ± 7.7	74.4	Korea
		WMC 1–4	160				62.2 ± 7.4	70.0	
		WMC 0	304				57.3 ± 6.4	71.1	
Kepplinger et al. [18]	WMC	WMC (+)	28	WMH	PSG	AHI ≥ 5	66.6 ± 7.3	50.0	Germany
		WMC (−)	28				62.1 ± 7.7	57.0	
Kumar et al. [13]	OSA	OSA (+)	23	Fiber integrity	PSG	AHI ≥ 15	44.4 ± 9.3	13.0	USA
		OSA (−)	23				45.3 ± 11.0	13.0	
Buterbaugh et al. [40]	OSA	OSA (+)	12	Cerebrovascular reactivity	PSG	AHI > 5	38.0 ± 5.0	0.0	USA
		OSA (−)	10				33.0 ± 5.0	0.0	
Chen et al. [39]	OSA	OSA (+)	20	Fiber integrity	PSG	AHI ≥ 5	38.6 ± 9.9	10.0	Taiwan
		OSA (−)	14				38.2 ± 9.9	21.4	

Table 1 (continued)

Study	Diagnosis	Group	Subject	Image targets	Sleep tools	Index of OSA	Mean age	Female (%)	Country
Baik et al. [38]	OSA	OSA (+)	235	WMH	PSG	AHI ≥ 5	60.8 ± 7.7	31.9	Korea
		OSA (−)	235				60.4 ± 7.6	32.8	
Castillo et al. [37]	SDB	AHI ≥ 15	9	WMH	PSG	AHI ≥ 15	75.1 ± 8.7	56.0	USA Ecuador
		AHI < 15	16				72.0 ± 5.8	50.0	
Patel et al. [20]	OSA	OSA (+)	34	WMH	Level 3 sleep monitor	RDI ≥ 15	68.4 ± 10.9	12.0	Canada
		OSA (−)	75				62.6 ± 13.1	36.0	
Tummala et al. [36]	OSA	OSA (+)	22	Mean kurtosis changes	PSG	AHI ≥ 5	49.2 ± 8.4	27.3	USA
		OSA (−)	26				45.6 ± 9.3	42.3	
Kacar et al. [35]	OSA	OSA (+)	47	ADC (apparent diffusion coefficient)	PSG	AHI ≥ 5	53.6 ± 8.5	14.9	Turkey
		OSA (−)	20				53.7 ± 9.1	45.0	
Rostanski et al. [21]	SDB	SDB (+)	33	WMH	MOS-SS	Waking short of breath	79.9 ± 5.7	75.8	USA
		SDB (−)	449				79.7 ± 5.2	70.8	
Lutsey et al. [34]	OSA	Mod./severe	60	WMH	PSG	AHI ≥ 5	62.5 ± 4.5	31.7	USA
							62.4 ± 4.9	37.5	
		Mild	88						
							61.1 ± 5.2	70.1	
		OSA (−)	164						
Choi et al. [33]	WMC	WMC (+)	192	WMH	PSG	AHI ≥ 5	63.5 ± 7.2	53.6	Korea
		WMC (−)	228				59.4 ± 6.7	64.5	
Song et al. [32]	WMC	WMC (+)	25	WMH	PSG	AHI ≥ 5	68.0 ± 7.0	52.0	Korea
		WMC (−)	145				57.0 ± 13.0	41.4	
Maurousset et al. [31]	OSA	OSA (+)	15	WMH	PSG	AHI ≥ 5	72.0	46.7	France
							62.4	33.3	
		OSA (−)	12						
Del Brutto et al. [42]	OSA	OSA (+)	27	WMH	PSG	AHI ≥ 15	72.4 ± 8.3	59.3	USA
							72.3 ± 6.4	67.1	
		OSA (−)	70						
Kerner et al. [19]	OSA	OSA (+)	10	WMH	STOP-Bang scale	AHI ≥ 5	69.9 ± 8.0	20.0	USA
		OSA (−)	15				71.1 ± 10.0	66.7	
Yilmaz et al. [30]	OSA	Severe	99	WMH	PSG	AHI ≥ 5	57.0 ± 14.0	19.0	Turkey
		Moderate	55				55.0 ± 12.0	29.0	
		Mild	69				53.0 ± 12.0	44.0	
		OSA (−)	74				44.0 ± 13.0	50.0	

AHI apnea/hypopnea index, *ARWMC* age-related white matter changes, *MOS-SS* Medical Outcomes Study-Sleep Scale, *ODI* oxygen desaturation index, *OSA* obstructive sleep apnea, *PSG* polysomnography, *RDI* respiratory disturbance index, *SDB* sleep disordered breathing, *WMC* white matter changes, *WMH* white matter hyperintensities, *UK* United Kingdom, *USA* United States of America

Subgroup meta-analysis

All of the recruited studies in this part of the meta-analysis identified cerebral hyperintensities based on T2/FLAIR images rather than white matter fiber integrity, and revealed the same results as the main meta-analysis.

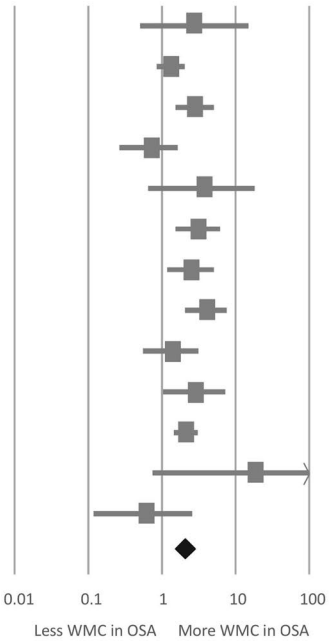
Meta-analysis investigating the severity of WMCs in the patients with OSA and controls without OSA

Among the nine eligible articles comparing the severity of WMCs in patients with OSA and controls without OSA [12, 13, 20, 21, 34–36, 39, 41], the meta-analysis results revealed a significantly higher severity of WMCs in the patients with OSA than in the controls without OSA ($k = 12$, Hedges' $g = 0.23$, 95% CI 0.06–0.40, $p = 0.009$) (Fig. 2b) with significant heterogeneity (Q value = 22.77, $df = 11$, $p = 0.019$; $I^2 = 51.7\%$) but borderline publication bias via Egger's regression test (t value = 2.31, $df = 10$, $p = 0.043$). Duval and Tweedie's trim and fill test revealed no need to adjust the estimated ESs.

The meta-regression procedure showed that there were only significant positive associations between the severity of WMCs in the patients and prevalence rate of hypertension (slope = 0.0082, $k = 8$, $p = 0.047$) and DM (slope = 0.0198, $k = 8$, $p = 0.044$), but not between the severity of WMCs and

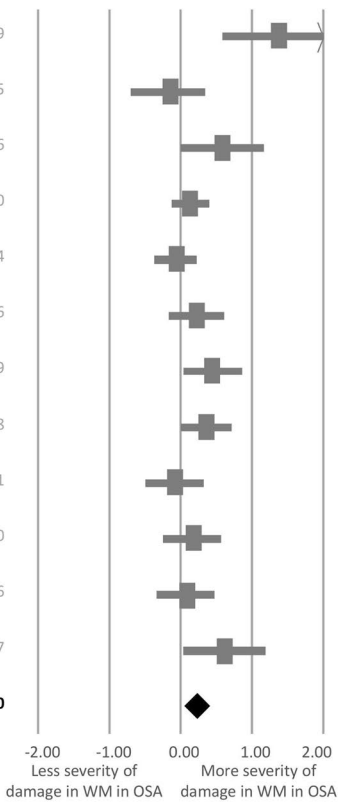
A

Study name	Outcome	Odds ratio	Lower limit	Upper limit	*p*-Value	Relative weight
Castillo et al[37] (2015)	Moderate-to-severe WMH	2.750	0.509	14.860	0.240	2.80
Choi et al[33] (2016) mild OSA	White matter abnormality	1.313	0.853	2.019	0.216	13.76
Choi et al[33] (2016) moderate/severe OSA	White matter abnormality	2.786	1.538	5.044	0.001	11.04
Davies et al[10] (2001)	Prevalence of MRI abnormalities	0.659	0.268	1.620	0.364	7.18
Maurousset et al[31] (2017)	Brain MRI leukoaraiosis	3.429	0.656	17.927	0.144	2.90
Yilmaz et al[30] (2017) mild OSA	WMC (presence)	3.073	1.542	6.121	0.001	9.65
Yilmaz et al[30] (2017) moderate OSA	WMC (presence)	2.451	1.185	5.069	0.016	9.15
Yilmaz et al[30] (2017) severe OSA	WMC (presence)	3.961	2.081	7.539	0.000	10.30
Patel et al[20] (2015)	DWI lesion	1.318	0.560	3.102	0.527	7.63
Del Brutto et al[42] (2017)	Moderate-to-severe WMH	2.750	1.047	7.222	0.040	6.56
Baik et al[38] (2015)	Diagnosis of WMH on brain MRI	2.116	1.461	3.064	0.000	14.81
Kerner et al[19] (2017)	Microvascular lesion severity	16.361	0.753	355.345	0.075	0.94
Buterbaugh et al[40] (2015)	White matter lesions	0.552	0.119	2.557	0.448	3.29
Total		**2.058**	**1.516**	**2.795**	**0.000**	**100.00**



B

Study name	Outcome	Hedges' *g*	Lower limit	Upper limit	*p*-Value	Relative weight
Chen et al[39] (2015)	White matter integrity	1.326	0.589	2.064	0.000	4.09
Kacar et al[35] (2016)	apparent diffusion coefficient values	-0.180	-0.698	0.338	0.496	6.65
Kumar et al[13] (2014)	myelin and axonal integrity	0.581	0.001	1.162	0.050	5.76
Lutsey et al[34] (2016) mild OSA	White matter hyperintensity volume	0.137	-0.121	0.396	0.298	12.30
Lutsey et al[34] (2016) moderate/severe OSA	White matter hyperintensity volume	-0.072	-0.367	0.223	0.633	11.34
Macey et al[12] (2008)	Fiber integrity	0.220	-0.164	0.605	0.262	9.16
Patel et al[20] (2015)	Normalized WMH volume (%)	0.452	0.045	0.858	0.030	8.69
Rostanski et al[21] (2016)	White matter hyperintensity volume	0.358	0.004	0.711	0.047	9.88
Schulz et al[41] (2013) Q2	leukoaraiosis	-0.086	-0.492	0.320	0.677	8.71
Schulz et al[41] (2013) Q3	leukoaraiosis	0.158	-0.243	0.560	0.439	8.80
Schulz et al[41] (2013) Q4	leukoaraiosis	0.067	-0.336	0.471	0.743	8.76
Tummala et al[36] (2016)	Global MK values	0.615	0.043	1.187	0.035	5.87
Overall		**0.228**	**0.057**	**0.399**	**0.009**	**100.00**



◀ **Fig. 2** **a** Meta-analysis of prevalence rate of WMC in patients with OSA and controls without OSA; **b** meta-analysis of severity of WMC in patients with OSA and controls without OSA; **c** meta-analysis of severity of AHI in patients with WMC and controls without WMC; **d** meta-analysis of prevalence rate of mild OSA in patients with WMC and controls without WMC and; **e** meta-analysis of prevalence rate of moderate/severe OSA in patients with WMC and controls without WMC. Panel **a** indicated significantly higher prevalence rate of WMC in patients with OSA than controls without OSA (OR 2.06, 95% CI 1.52–2.80, $p<0.001$), panel **b** showed significantly higher severity of WMC in patients with OSA than controls without OSA (Hedges' $g=0.23$, 95% CI 0.06–0.40, $p=0.009$), panel **c** suggested significantly higher AHI in patients with WMC than controls without WMC (Hedges' $g=0.54$, 95% CI 0.31–0.78, $p<0.001$), panel **d** found that there was no any significantly different prevalence rate of mild OSA in patients with WMC and controls without WMC (OR 0.71, 95% CI 0.20–2.54, $p=0.603$), and panel **e** revealed significantly higher prevalence rate of moderate/severe OSA in patients with WMC than controls without WMC (OR 2.86, 95% CI 1.44–5.66, $p=0.003$). *AHI* apnea–hypopnea index, *CI* confidence interval, *DWI* diffusion-weighted imaging, *MA* meta-analysis, *MK* mean kurtosis, *MRI* magnetic resonance imaging, *OR* odds ratio, *OSA* obstructive sleep apnea, *WMC* white matter change, *WMH* white matter hyper-intensity

other clinical variables including mean age ($p=0.262$), female proportion ($p=0.639$), BMI ($p=0.616$), and AHI ($p=0.060$).

Subgroup meta-analysis

Among the studies referring to white matter hyperintensities (WMHs)/small vessel disease [20, 21, 34, 41], the meta-analysis results revealed no significant differences in the severity of WMCs in the patients with OSA compared to the controls without OSA ($k=7$, Hedges' $g=0.13$, 95% CI −0.01 to 0.28, $p=0.067$). However, the severity of WMCs was significantly higher in the patients with OSA compared to the controls without OSA in the studies referring to neural fiber integrity ($k=5$, Hedges' $g=0.46$, 95% CI 0.03–0.89, $p=0.036$) [12, 13, 35, 36, 39].

Meta-analysis investigating the differences in AHI in the patients with WMCs and controls without WMCs

Among the four eligible articles comparing differences in AHI between the patients with WMCs and controls without WMCs [9, 18, 32, 33], the meta-analysis results revealed a significantly higher AHI in the patients with WMCs compared to the controls without WMCs ($k=5$, Hedges' $g=0.54$, 95% CI 0.31–0.78, $p<0.001$; difference in means = 5.289, 95% CI 2.46–8.12, $p<0.001$) (Fig. 2c) with significant heterogeneity (Q value = 12.57, $df=4$, $p=0.014$; $I^2=68.2\%$), but no significant publication bias by visual examination of the funnel plot (supplement figure 1A).

The meta-regression procedure showed a significant positive association only between the severity of AHI and prevalence rate of hypertension (slope = 0.0172, $k=5$, $p=0.001$). There were no significant associations between the severity of AHI and other clinical variables including mean age ($p=0.388$), female proportion ($p=0.214$), and prevalence rate of DM ($p=0.498$).

Subgroup meta-analysis

All of the recruited studies in this part of meta-analysis identified WMCs in neuroimaging referring to small vessel disease rather than neural fiber integrity, which revealed the same results as the main meta-analysis.

Meta-analysis investigating the prevalence rate of mild OSA in the patients with WMCs and controls without WMCs

Among the three eligible articles comparing the prevalence rate of mild OSA in the patients with WMCs and controls without WMCs [9, 11, 18], the meta-analysis results revealed no significant difference in the prevalence rate of mild OSA in the patients with WMCs compared to the controls without WMCs ($k=5$, OR 0.71, 95% CI 0.20–2.54, $p=0.603$) (Fig. 2d) with significant heterogeneity (Q value = 39.12, $df=4$, $p<0.001$; $I^2=89.8\%$) but no publication bias by visual examination of the funnel plot (supplement figure 1B).

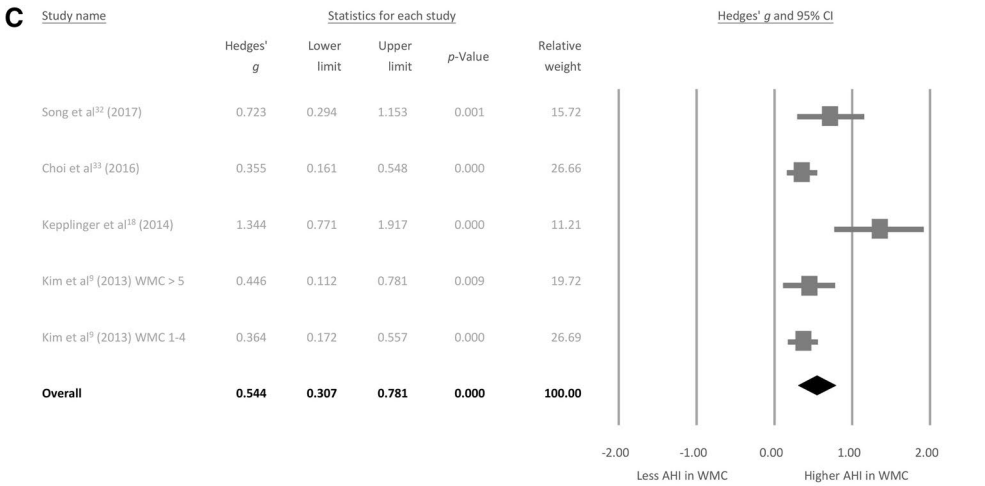
The meta-regression procedure showed no significant associations between the prevalence rate of mild OSA and other clinical variables including mean age ($p=0.614$), female proportion ($p=0.455$), prevalence rate of hypertension ($p=0.277$), and prevalence rate of DM ($p=0.940$).

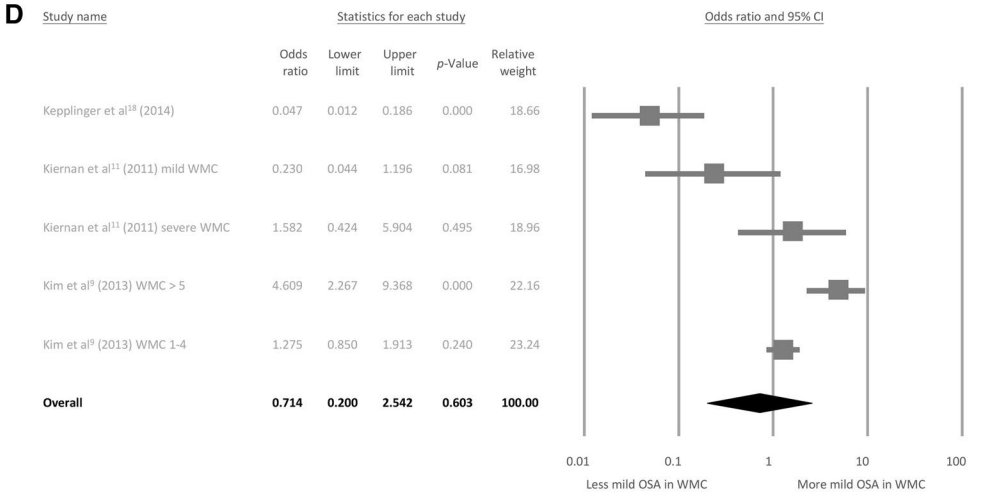
Subgroup meta-analysis

All of the recruited studies in this part of the meta-analysis identified WMCs in neuroimaging referring to WMHs/small vessel disease rather than neural fiber integrity, which revealed the same results as main meta-analysis.

Meta-analysis investigating the prevalence rate of moderate-to-severe OSA in the patients with WMCs and controls without WMCs

Among the three eligible articles comparing the prevalence rate of moderate-to-severe OSA in the patients with WMCs and controls without WMCs [9, 11, 18], the meta-analysis results revealed a significantly higher prevalence rate of moderate-to-severe OSA in the patients with WMCs compared to the controls without WMCs ($k=5$, OR 2.86, 95% CI 1.44–5.66, $p=0.003$) (Fig. 2e) without significant heterogeneity (Q value = 8.17, $df=4$, $p=0.085$; $I^2=51.1\%$) but significant publication bias by visual examination of the funnel





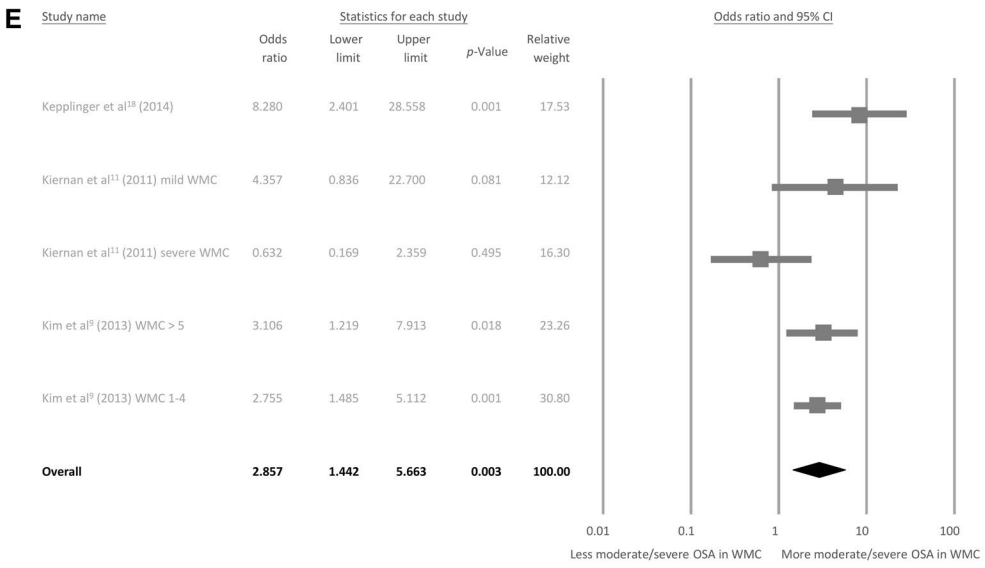


Fig. 2 (continued)

plot (supplement figure 1C). The adjusted estimated ESs according to Duval and Tweedie's trim and fill test remained significant (OR 2.27, 95% CI 1.10–4.67).

The meta-regression procedure showed no significant associations between the prevalence rate of moderate-to-severe OSA and other clinical variables including mean age ($p = 0.718$), female proportion ($p = 0.543$), prevalence rate of hypertension ($p = 0.825$), and prevalence rate of DM ($p = 0.406$).

Subgroup meta-analysis

All of the recruited studies in this part of the meta-analysis identified WMCs in neuroimaging referring to WMHs/small vessel disease rather than neural fiber integrity, which revealed the same results as the main meta-analysis.

Discussion

In the current study, we systemically reviewed related research articles and verified the bidirectional relationship between OSA and WMCs. According to the pooled results of the enrolled studies, the patients with OSA had a significantly higher prevalence rate ($p < 0.001$, OR 2.06, 95% CI 1.52–2.80) and higher severity of WMCs, particularly in terms of white matter integrity, than those without OSA. The multivariate meta-regression showed that the severity of WMCs in the patients with OSA was only positively correlated with DM (slope = 0.02, $p = 0.044$) or hypertension (slope = 0.01, $p = 0.047$), but not with other variables such as mean age, female gender, BMI, or AHI. Furthermore, the patients with identified WMCs had a significantly higher AHI and a higher prevalence rate of moderate-to-severe OSA ($p = 0.003$, OR 2.86, 95% CI 1.44–5.66) than the controls.

Associations between sleep-disordered breathing and cerebral structural changes on MRI have been documented in previous epidemiological studies; however their results have been inconsistent. In a cross-sectional and longitudinal cohort research, individuals (mean age 77 years, 58% women) with progressive white matter disease tended to have a significantly higher number of central but not obstructive apneas on polysomnography-based home sleep analysis [43]. In addition, larger WMH volumes have been observed in community-dwelling older adults (mean age 79.7 years, 71% women) with self-reported sleep-disordered breathing [21]. More specifically, an increasing number of recent studies has provided evidence of the relationship between OSA and cerebral WMCs. Population-based studies have reported that the prevalence of OSA and mean AHI are higher in patients with WMHs [9], and also positive associations between WMHs and OSA independently of gene–environment interactions [38].

In addition to WMHs on T2/FLAIR sequences, white matter integrity has also been increasingly used to evaluate patients with sleep disturbances and OSA. The degree of fiber integrity can be illustrated in DTI images, and abnormal neuronal integrity has been demonstrated in vulnerable regions such as the limbic system, basal ganglia, cerebellar and some cerebral cortices [12, 13]. Impairment in white matter integrity, as represented by DTI-related indices, has been associated with an increased clinical severity of OSA [39]. Moreover, the development of WMHs has been reported to be preceded by quantifiable changes even in normal-appearing white matter, which indicates that decreased white matter integrity may be a precursor to WMHs [44].

An important aspect that needs to be emphasized and requires further clarification is the association between cerebral WMCs and the severity of OSA. Among the included studies of this meta-analysis, a positive correlation between the level of AHI and WMCs was observed. Kim et al. reported a significant increasing trend in WMCs with an increasing severity of OSA in older individuals of the general population, and that patients with moderate-to-severe OSA (AHI $\geq$ 15) had a twofold increased risk of WMCs [9]. Kepplinger et al. found that in patients with acute cerebral ischemia, the AHI and extent of leukoaraiosis were moderately correlated even after adjusting for age and arterial hypertension, and that AHI was an independent predictor of moderate-to-severe leukoaraiosis [18]. Furthermore, Choi et al. observed an increased risk of developing WMCs with moderate-to-severe OSA compared to mild OSA among the elderly with a shortened telomere length, which is a candidate biomarker of ageing [33]. Song et al. also reported that moderate-to-severe OSA was positively associated with multiple indicators of cerebral small vessel disease, including white matter hyperintensities, cerebral microbleeds, and perivascular spaces [32]. Based on these findings, the clinical severity of OSA may play a more important role than the presence of OSA in mediating the pathogenesis of WMCs.

The major clinical implication of this meta-analysis is to offer significant evidence for the high prevalence rate of cerebral WMCs in patients with OSA. The presence of these subclinical cerebrovascular lesions in patients with OSA is thought to play an important role in the preconditioning phase of symptomatic cerebrovascular disease [8]. A prior review, including 46 prospective longitudinal studies, indicated that WMCs may predict an increased risk of stroke, dementia and mortality [6]. Another review, including both cross-sectional ($n = 23$) and longitudinal studies ($n = 14$), reported that the presence of WMCs was significantly associated with coincident global cognitive deficits, and that the progression of WMCs was associated with a greater

subsequent cognitive decline, particularly in attention and executive functioning [45]. The neuropsychological effects of OSA itself may also result in cognitive and functional impairments. Castronovo et al. found that after 12 months of continuous positive airway pressure treatment, patients with OSA had appreciable improvements in both white matter integrity and cognitive deficits [46].

There are several limitations to this study. First, the number of articles included into our final meta-analysis was relatively small. Second, the heterogeneity of primary outcomes, including the burden of WMCs and the severity of OSA, was significant. Heterogeneity of the imaging modalities, study designs and setting of the enrolled studies also makes the interpretation of the published data difficult. Third, we could not further classify the WMCs according to specific functional localization of cerebral hemispheres and lobes based on the current data. One additional key limitation in the literature should be addressed was the different scoring criteria for hypopneas, which can determine a large part of severity, of OSA diagnosis. This has evolved over the years, with many standards, and an argument can be made for that driven by hypoxia or by arousals, as both are disruptive to cerebrovascular biology. In addition, the eligible articles enrolled in our meta-analysis were mostly retrospective or cross-sectional studies. Due to the scarcity of longitudinal studies recruited in our analysis, etiological correlations inherent to longitudinal effect estimates between OSA and WMCs still need to be confirmed during the course of long-term follow-up.

In conclusion, this study provides comprehensive evidence of a significant bidirectional relationship between OSA and cerebral WMCs. A significantly higher prevalence of WMCs in patients with moderate-to-severe OSA raises a therapeutic concern for clinicians, and managing risk factors may prevent the development of stroke and dementia. Future large-scale randomized controlled trials with a longitudinal design are essential, especially to further evaluate the effect of treatment in patients with OSA.

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Compliance with ethical standards

Conflicts of interest There was no conflict of interests among the authors.

Ethical standard This study was approved by the Institutional Review Board of Tri-Service General Hospital (TSGHIRB: B-105-12).

References

1. Jackson CL, Redline S, Emmons KM (2015) Sleep as a potential fundamental contributor to disparities in cardiovascular health. Annu Rev Public Health 36:417–440
2. Daulatzai MA (2015) Evidence of neurodegeneration in obstructive sleep apnea: relationship between obstructive sleep apnea and cognitive dysfunction in the elderly. J Neurosci Res 93(12):1778–1794
3. Kato M, Roberts-Thomson P, Phillips BG et al (2000) Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation 102(21):2607–2610
4. Khayat R, Patt B, Hayes D Jr (2009) Obstructive sleep apnea: the new cardiovascular disease. Part I: obstructive sleep apnea and the pathogenesis of vascular disease. Heart Fail Rev 14(3):143–153
5. Ovbiagele B, Saver JL (2006) Cerebral white matter hyperintensities on MRI: current concepts and therapeutic implications. Cerebrovasc Dis 22(2–3):83–90
6. Debette S, Markus HS (2010) The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 341:c3666
7. Wardlaw JM, Smith C, Dichgans M (2013) Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol 12(5):483–497
8. Nishibayashi M, Miyamoto M, Miyamoto T, Suzuki K, Hirata K (2008) Correlation between severity of obstructive sleep apnea and prevalence of silent cerebrovascular lesions. J Clin Sleep Med 4(3):242–247
9. Kim H, Yun CH, Thomas RJ et al (2013) Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. Sleep 36(5):709-715B
10. Davies CW, Crosby JH, Mullins RL et al (2001) Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. Sleep 24(6):715–720
11. Kiernan TE, Capampangan DJ, Hickey MG, Pearce LA, Aguilar MI (2011) Sleep apnea and white matter disease in hypertensive patients: a case series. Neurologist 17(5):289–291
12. Macey PM, Kumar R, Woo MA, Valladares EM, Yan-Go FL, Harper RM (2008) Brain structural changes in obstructive sleep apnea. Sleep 31(7):967–977
13. Kumar R, Pham TT, Macey PM, Woo MA, Yan-Go FL, Harper RM (2014) Abnormal myelin and axonal integrity in recently diagnosed patients with obstructive sleep apnea. Sleep 37(4):723–732
14. Morrell MJ, Jackson ML, Twigg GL et al (2010) Changes in brain morphology in patients with obstructive sleep apnoea. Thorax 65(10):908–914
15. Torelli F, Moscufo N, Garreffa G et al (2011) Cognitive profile and brain morphological changes in obstructive sleep apnea. Neuroimage 54(2):787–793
16. Stroup DF, Berlin JA, Morton SC et al (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283(15):2008–2012
17. Wells GA, Shea B, O'Connell D et al (2011) The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa Hospital Research Institute, Ottawa
18. Kepplinger J, Barlinn K, Boehme AK et al (2014) Association of sleep apnea with clinically silent microvascular brain tissue changes in acute cerebral ischemia. J Neurol 261(2):343–349
19. Kerner NA, Roose SP, Pelton GH et al (2017) Association of obstructive sleep apnea with episodic memory and cerebral

microvascular pathology: a preliminary study. Am J Geriatr Psychiatry 25(3):316–325
20. Patel SK, Hanly PJ, Smith EE, Chan W, Coutts SB (2015) Nocturnal hypoxemia is associated with white matter hyperintensities in patients with a minor stroke or transient ischemic attack. J Clin Sleep Med 11(12):1417–1424
21. Rostanski SK, Zimmerman ME, Schupf N et al (2016) Sleep disordered breathing and white matter hyperintensities in community-dwelling elders. Sleep 39(4):785–791
22. Borenstein M, Hedges LV, Higgins JP, Rothstein HR (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 1(2):97–111
23. Tobias A (1999) Assessing the influence of a single study in meta-analysis. Stata Tech Bull 47:15–17
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560
25. Borenstein M, Higgins JP, Hedges LV, Rothstein HR (2017) Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. Res Synth Methods 8(1):5–18
26. Higgins JPT, Green S (2011) 10.4.3.1 Recommendations on testing for funnel plot asymmetry. In: Higgins JPT, Green S (eds) Cochrane handbook for systematic reviews of interventions (Version 5.1.0). The Cochrane Collaboration. http://handbook.cochrane.org/
27. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634
28. Duval S, Tweedie R (2000) Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56(2):455–463
29. Davey J, Turner RM, Clarke MJ, Higgins JP (2011) Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: a cross-sectional, descriptive analysis. BMC Med Res Methodol 11:160
30. Yilmaz Avci A, Avci S, Lakadamyali H, Can U (2017) Hypoxia and inflammation indicate significant differences in the severity of obstructive sleep apnea within similar apnea-hypopnea index groups. Sleep Breath 21(3):703–711
31. Maurousset A, De Toffol B, Praline J, Biberon J, Limousin N (2017) High incidence of obstructive sleep apnea syndrome in patients with late-onset epilepsy. Neurophysiol Clin 47(1):55–61
32. Song TJ, Park JH, Choi KH et al (2017) Moderate-to-severe obstructive sleep apnea is associated with cerebral small vessel disease. Sleep Med 30:36–42
33. Choi KM, Thomas RJ, Yoon DW, Lee SK, Baik I, Shin C (2016) Interaction between obstructive sleep apnea and shortened telomere length on brain white matter abnormality. Sleep 39(9):1639–1645
34. Lutsey PL, Norby FL, Gottesman RF et al (2016) Sleep apnea, sleep duration and brain MRI markers of cerebral vascular disease and Alzheimer's disease: the Atherosclerosis Risk in Communities Study (ARIC). PLoS One 11(7):e0158758
35. Kacar E, Sarinc Ulasli S, Gunay E et al (2016) Assessment of neural alterations in obstructive sleep apnoea syndrome: can apparent diffusion coefficient measurements be useful? Clin Respir J 10(2):189–197
36. Tummala S, Palomares J, Kang DW et al (2016) Global and regional brain non-Gaussian diffusion changes in newly diagnosed patients with obstructive sleep apnea. Sleep 39(1):51–57
37. Castillo PR, Del Brutto OH, Andrade Mde L, Zambrano M, Nader JA (2015) The association of sleep-disordered breathing with high cerebral pulsatility might not be related to diffuse small vessel disease. A pilot study. BMC Res Notes 8:500
38. Baik I, Seo HS, Yoon D, Kim SH, Shin C (2015) Associations of sleep apnea, NRG1 polymorphisms, alcohol consumption, and cerebral white matter hyperintensities: analysis with genome-wide association data. Sleep 38(7):1137–1143
39. Chen HL, Lu CH, Lin HC et al (2015) White matter damage and systemic inflammation in obstructive sleep apnea. Sleep 38(3):361–370
40. Buterbaugh J, Wynstra C, Provencio N, Combs D, Gilbert M, Parthasarathy S (2015) Cerebrovascular reactivity in young subjects with sleep apnea. Sleep 38(2):241–250
41. Schulz UG, Mason RH, Craig SE et al (2013) Leukoaraiosis on MRI in patients with minimally symptomatic obstructive sleep apnoea. Cerebrovasc Dis 35(4):363–369
42. Del Brutto OH, Mera RM, Zambrano M, Castillo PR (2017) Relationship between obstructive sleep apnea and neuroimaging signatures of cerebral small vessel disease in community-dwelling older adults. The Atahualpa Project. Sleep Med 37:10–12
43. Robbins J, Redline S, Ervin A, Walsleben JA, Ding J, Nieto FJ (2005) Associations of sleep-disordered breathing and cerebral changes on MRI. J Clin Sleep Med 1(2):159–165
44. de Groot M, Verhaaren BF, de Boer R et al (2013) Changes in normal-appearing white matter precede development of white matter lesions. Stroke 44(4):1037–1042
45. Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E (2014) Presence and progression of white matter hyperintensities and cognition: a meta-analysis. Neurology 82(23):2127–2138
46. Castronovo V, Scifo P, Castellano A et al (2014) White matter integrity in obstructive sleep apnea before and after treatment. Sleep 37(9):1465–1475