SLEEPJ, 2020, 1–10

doi: 10.1093/sleep/zsz264
Advance Access Publication Date: 7 November 2019
Original Article

ORIGINAL ARTICLE

Association of obstructive sleep apnea and cerebral small vessel disease: a systematic review and meta-analysis

Yuhong Huang[1,†], Chunsong Yang[2,†], Ruozhen Yuan[1], Ming Liu[1,*], Zilong Hao[1,*]

[1]Department of Neurology, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan 610041, China and [2]Department of Pharmacy, Evidence-Based Pharmacy Center, West China Second Hospital, Sichuan University, Chengdu, Sichuan 610041 China

*Corresponding author. Zilong Hao, Center of Cerebrovascular Disease, Department of Neurology, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan 610041, China. Email: zhilong1983@126.com; or Ming Liu, Email: wyplmh@hotmail.com

†These authors contributed equally to this study.

Abstract

Study Objectives: The objective of the present study was to investigate the association between obstructive sleep apnea (OSA) and the presence of various neuroimaging marker of cerebral small vessel disease (CSVD).

Methods: We systematically searched PubMed, Embase, Web of Science, Scopus, and Cochrane library (from inception to May 2019) for studies evaluating the association between OSA and CSVD, which included white matter hyperintensities (WMH), silent brain infarction (SBI), cerebral microbleeds (CMBs), and perivascular spaces (PVS). Pooled odds ratios (ORs) with 95% confidence interval (CIs) were estimated using random-effects meta-analysis.

Results: After screening 7290 publications, 20 studies were finally included involving 6036 subjects. The sample size ranged from 27 to 1763 (median 158, interquartile range: 67–393). The meta-analysis showed that moderate to severe OSA was positively associated with WMH (13 studies, n = 4412, OR = 2.23, 95% CI = 1.53 to 3.25, I^2 = 80.3%) and SBI (12 studies, n = 3353, OR 1.54, 95% CI = 1.06 to 2.23, I^2 = 52%). There was no association with CMBs (three studies, n = 342, OR = 2.17, 95% CI = 0.61 to 7.73, I^2 = 60.2%) or PVS (two studies, n = 267, OR = 1.56, 95% CI = 0.28 to 8.57, I^2 = 69.5%). There was no relationship between mild OSA and CSVD.

Conclusion: Current evidence suggests that moderate to severe sleep apnea is positively related to WMH and SBI, but not CMBs or PVS, which suggests that OSA may contribute to the pathogenesis of CSVD. Further large cohort studies should be prioritized to confirm the findings.

Statement of Significance

Cerebral small vessel disease (CSVD) is often regarded as an incidental finding on brain magnetic resonance imaging (MRI) and manifests as white matter hyperintensities (WMH), silent brain infarction (SBI), cerebral microbleeds (CMBs), and perivascular spaces (PVS). CSVD is associated with an increased risk of stroke, cognitive impairment, and death. It is important to identify the risk factors for CSVD to ensure early prevention. This systematic review includes 20 studies that indicate that moderate to severe sleep apnea is positively related to WMH and SBI but not CMBs or PVS. OSA may be a potential risk factor for CSVD, which may guide efforts to prevent CSVD. Long-term follow-up studies are required to confirm the relationship between OSA and CSVD.

Key words: obstructive sleep apnea; white matter hyperintensities; silent brain infarction; cerebral microbleeds; cerebral small vessel disease

Submitted: 1 May, 2019; **Revised:** 30 August, 2019

Introduction

Cerebral small vessel disease (CSVD) is often regarded as an incidental finding on brain magnetic resonance imaging (MRI) and manifests as white matter hyperintensities (WMH), silent brain infarction (SBI), cerebral microbleeds (CMBs), and perivascular spaces (PVS) [1, 2]. Recent meta-analyses have indicated that CSVD is associated with an increased risk of overt stroke, cognitive impairment or dementia, and death [3–6]. With the aging of the population and the increased use of advanced brain imaging modalities, the prevalence of CSVD is expected to increase among asymptomatic individuals [7]. It is important to identify the risk factors for CSVD to ensure early prevention and decrease the occurrence of CSVD and its complications. Age, hypertension, diabetes mellitus, and smoking are regarded as risk factors for CSVD [2, 8]. However, these traditional risk factors do not fully explain the occurrence of CSVD [9].

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of hypoxia during sleep and is a major public health problem because of its high prevalence in the general population [10]. Recent studies have shown that severe OSA is associated with hypertension, atherosclerosis, cardiovascular disease, and stroke [10–13]. These data suggest that OSA might be associated with an increased risk of CSVD by promoting the occurrence of hypertension and endothelial dysfunction. However, conflicting results have been reported in previous studies investigating the association between OSA and neuroimaging markers of CSVD. While some studies found no association between OSA and CSVD, others indicated that moderate to severe OSA was an independent risk factor for leukoaraiosis and SBI [14–18]. In addition, most of those studies involved relatively small samples. Therefore, we conducted a systematic review and meta-analysis to investigate the association between OSA and the presence of various neuroimaging marker of CSVD.

Methods

Search strategy and eligible studies

We systematically searched PubMed, Embase, Web of Science, Scopus, and Cochrane library (from inception to May 2019) for observational studies (cohort, cross-sectional, and case-control studies) evaluating the association between OSA and CSVD (WMH, SBI, CMBs, or PVS). We conducted the study in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines [19] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20]. The Boolean search used the following terms to search for relevant studies: obstructive sleep apnea, obstructive sleep apnea syndrome, sleep-disordered breathing, sleep-related breathing disorder, sleep disorders, sleep apnea, cerebral small vessel disease, white matter hyperintensities, white matter lesions, white matter abnormalities, white matter disease, white matter change, leukoaraiosis, silent lacunar infarctions, silent brain infarction, silent cerebral infarct, lacunar infarctions, lacunae lesions, cerebral microbleeds, perivascular spaces, silent cerebrovascular disease, silent cerebrovascular lesions, stroke, cerebrovascular disease, brain injury, subclinical brain damage, and subclinical cerebrovascular disease. The reference lists of the included studies were also checked. The following inclusion criteria were applied: (1) studies involved any type of participants; (2) studies investigated the association between OSA and CSVD, including WMH, SBI, CMBs, and PVS; (3) OSA was evaluated by objective methods, such as polysomnography (PSG) or pulse oximetry; (4) imaging markers of CSVD were measured using either MRI or computed tomography (CT); (5) results were reported as odds ratio (OR) or risk ratio (RR) with 95% confidence interval (CI), or the OR or RR could be calculated. Studies were excluded if: (1) WMH were measured by advanced MRI methods, such as magnetic resonance spectroscopy for metabolic status or diffusion tensor imaging for the region of interest of WMH; (2) OSA was diagnosed based only on clinical symptoms or scales; or (3) the study was a case report, case series, conference proceeding, or anything written in a language other than English. If publications involved overlapping study populations, only the most relevant or recent was included. Because this was a systematic review of published studies, ethical approval was not required.

Study selection and data extraction

Two trained neurologists (R.Y. and Z.H.) screened the titles and abstracts of all documents and excluded obviously irrelevant studies. The full articles were obtained for further evaluation if screening of the titles and abstracts was considered insufficient. Two trained neurologists (Y.H. and Z.H.) independently read the full-text articles and performed data extraction. The following information was extracted from each study using a predesigned data extraction form: (1) authors and publication year; (2) study design and sample; (3) baseline characteristics of participants, such as age and sex; (4) assessment and diagnostic criteria of OSA; (5) assessment of CSVD; (6) reported or calculated OR and 95% CI for CSVD; and (7) adjusted confounders in individual studies. Discrepancies at any stage were resolved by discussion.

Quality assessment

Two reviewers (Y.H. and C.Y.) independently conducted the quality assessment. The quality of cross-sectional studies was assessed using the checklist for analytical cross-sectional studies developed by the Joanna Briggs Institute (JBI) [21]. This checklist includes the following eight items: (1) were the criteria for inclusion in the sample clearly defined? (2) Were the study subjects and the setting described in detail? (3) Was the exposure measured in a valid and reliable way? (4) Were objective, standard criteria used for measurement of the condition? (5) Were confounding factors identified? (6) Were strategies to deal with confounding factors stated? (7) Were the outcomes measured in a valid and reliable way? (8) Was appropriate statistical analysis used? Each item was classified as Yes, No, Unclear, or Not applicable. We assessed the quality of cohort and case-control studies using the Newcastle–Ottawa Scale (NOS). This scale is based on three aspects of the study: (1) selection of participants, (2) comparability of study groups, and (3) outcome. The highest-quality study receives nine stars [22]. Any disagreements were resolved by discussion.

Statistical methods

The OR and 95% CI were calculated for four types of CSVD if two or more studies were included. We used the I^2 test to evaluate heterogeneity. If I^2 was more than 50%, we considered the study to have substantial heterogeneity. A random-effects model was used regardless of the extent of heterogeneity. We conducted subgroup analysis based on the following factors: (1) different criteria of sleep apnea (apnea–hypopnea index [AHI], oxygen desaturation index [ODI], more than 4% falls in arterial saturation (SaO_2) per hour]; (2) study design (cohort, cross-sectional, and case-control studies); (3) source of participants (population-based study or sleep clinic); (4) studies with or without adjusted confounders, (5) region of study (Asia or non-Asia); (6) mean or median age reported in individual study (<60, 60–69, and ≧70 years). These factors may contribute to the heterogeneity. Potential publication bias was investigated using Begg's and Egger's tests as well as funnel plots. We also conducted a sensitivity analysis by excluding one study at a time. All analyses were conducted with Stata 11 software (StataCorp, College Station, TX) and R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Data availability

The data supporting the findings were extracted from the published studies. All the data are available from the corresponding author upon reasonable request.

Results

Literature search

The search and study selection processes are shown in Figure 1. Briefly, 7290 publications were identified after the initial literature search. After reading the titles and abstracts, 75 publications were identified for further assessment. Of these, we excluded 55 studies for different reasons. The characteristics and main results of these excluded studies are shown in Supplementary Table S1. In the end, 20 studies involving 6036 patients were included in this systematic review [14–18, 23–37].

Characteristics of included studies

The detailed characteristics of the included studies are shown in Table 1 and Supplementary Table S2. Of the 20 included studies, 10 were performed in Asia [14, 15, 23, 24, 27, 28, 30, 32, 34, 37], 5 in Europe [25, 26, 29, 33, 35], and 5 in the United States [16–18, 31, 36]. With respect to the study design, 15 studies were cross-sectional studies [14–16, 23–32, 35, 36], 2 were prospective cohort studies [17, 18], and 3 were case-control studies [33, 34, 37]. We categorized the studies into groups of WMH, SBI, CMBs, and PVS according to the type of CSVD metric(s) reported in individual studies. Most studies reported on the association between OSA and one type of CSVD, but two studies reported on the association between OSA and more than two types of CSVD (Supplementary Table S2) [15, 16]. Thirteen studies investigated

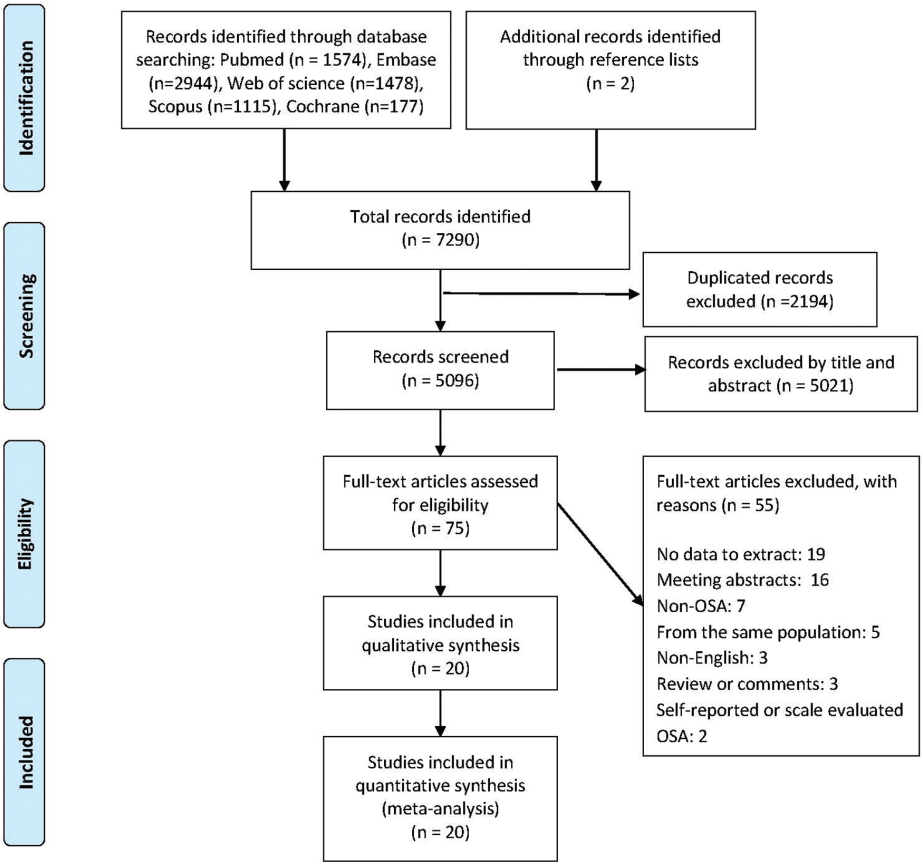

Figure 1. Flow diagram of literature search processing for the systematic review.

Table 1. The baseline characteristics of 20 included full-text studies

Author and year	Study design	Participants	Sample size	Age mean (years)	Men %	OSA assessment	OSA definition
Koo 2017 [14]	Cross-sectional study Korea	Sleep center without stroke history	75	60.5	60%	Overnight PSG	AHI ≧ 15, 36%
Song 2017 [15]	Cross-sectional study Korea	Sleep center stroke history: 5.3%	170	58 ± 13	57.1%	Overnight PSG	AHI ≧ 15, 44.1%
Del Brutto 2017 [16]	Cross-sectional study United States	Population-based study without stroke history	97	72.3 ± 7	35%	Overnight PSG	AHI ≧ 15, 27.8%
Lutsey 2016 [17]	Prospective cohort study United States Follow-up:15 years	Population-based study	312	61.7 ± 5	46%	Overnight PSG	AHI ≧ 15, 19%
Robbins 2005 [18]	Cross-sectional and cohort study United States	Population-based study	843	77 ± 4.3	42%	In-home PSG	AHI ≧ 15, 23.3%
Baik 2015 [23]	Cross-sectional study Korea	Population-based study without stroke history	1763	≈58	54.2%	Overnight PSG	AHI ≧ 15, 14.2%
Cho 2013 [24]	Cross-sectional study Korea	Population-based study without stroke history	746	59.25	33.8%	PSG	AHI ≧ 15, 12.06%
Alvarez-Sabín 2018 [25]	Matched cross-sectional study Spain	Hypertensive subjects without stroke history	183	64.1 ± 4.5	72.1%	Overnight PSG	AHI > 30, 40.4%
Kepplinger 2014 [26]	Cross-sectional study Germany	Patients with acute cerebral ischemia or TIA	56	64 ± 8	46%	Nocturnal respiratory polygraphy	AHI ≧ 15, 29%
Choi 2016 [27]	Cross-sectional study Korea	Community-based study	420	61.3 ± 7.2	40.7%	Overnight PSG	AHI ≧ 15, 14.3%
Yilmaz 2016 [28]	Cross-sectional study Turkey	Sleep center without stroke history	453	Median 51 (22–84)	69.2%	Overnight PSG	AHI≧15, 53.4%
Schulz 2013 [29]	Cross-sectional study UK	Substudy of the MOSAIC trial	183	57.7 ± 7.4	85.2%	Home oximetry	ODI > 7.5 (≧7.5 dips of>4% SaO_2/h)
Nishibayashi 2008 [30]	Cross-sectional study Japan	Sleep clinic without stroke history	192	50.6	88.5%	Overnight PSG	AHI ≧ 15, 77.1%
Kiernan 2011 [31]	Cross-sectional study United States	Sleep database Hypertensive patients without stroke history	62	67 ± 12	68%	PSG	AHI ≧ 15 or CPAP 69%
Eguchi 2005 [32]	Cross-sectional study Japan	Health screening	146	67.4 ± 9.0	26%	Pulse oximetry	ODI
Davies 2001 [33]	Case-control study UK	Case: sleep clinic Control: register of a general practice without stroke history	90	Case: 52 ± 10 Control: 52 ± 10	100%	Arterial oxygen saturation measurements	>4% falls in arterial saturation (Sa02)/h
Minoguchi 2007 [34]	Case-control study Japan	Case: NA Control: obesity without stroke history	65	Case: 51 ± 2 Control: 49 ± 3	100%	PSG	AHI ≧ 15, 48%
Maurousset 2017 [35]	Cross-sectional study France	Patients with late-onset epilepsy	27	67.8 ± 8.6	59.3%	PSG	AHI ≧ 15, 56%
Del Brutto 2019 [36]	Cross-sectional study United States	Population-based study	97	72.3 ± 7	35%	PSG	AHI ≧ 15, 28%
Gunbatar 2016 [37]	Case-control study Turkish	Sleep clinic without history of cerebrovascular disease	56	AHI (15–30): 50.14 AHI (≧30): 48.84 Control: 49.05	69.6%	PSG	AHI ≧ 15, 62.5%

TIA, transient ischemic attack; MOSAIC, Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular Trial; CPAP, continuous positive airway pressure; NA, not applicable.

the association between OSA and WMH [15, 16, 18, 23, 26–31, 33, 35, 37], 12 between OSA and SBI [15–18, 24–26, 28, 30, 32–34], 3 between OSA and CMBs [14–16], and 2 between OSA and PVS [15, 36]. The number of participants ranged from 27 to 1763 (median, 158 [interquartile range (IQR): 67–393]). The proportion of male participants ranged from 29% to 100%. Most studies (17/20, 85%) used PSG for assessment of OSA, and the others used pulse oximetry. For PSG measurement, the severity of OSA was measured by the AHI and classified as follows: normal, AHI of more than 5; mild OSA, AHI of 5 to more than 15; moderate OSA, AHI

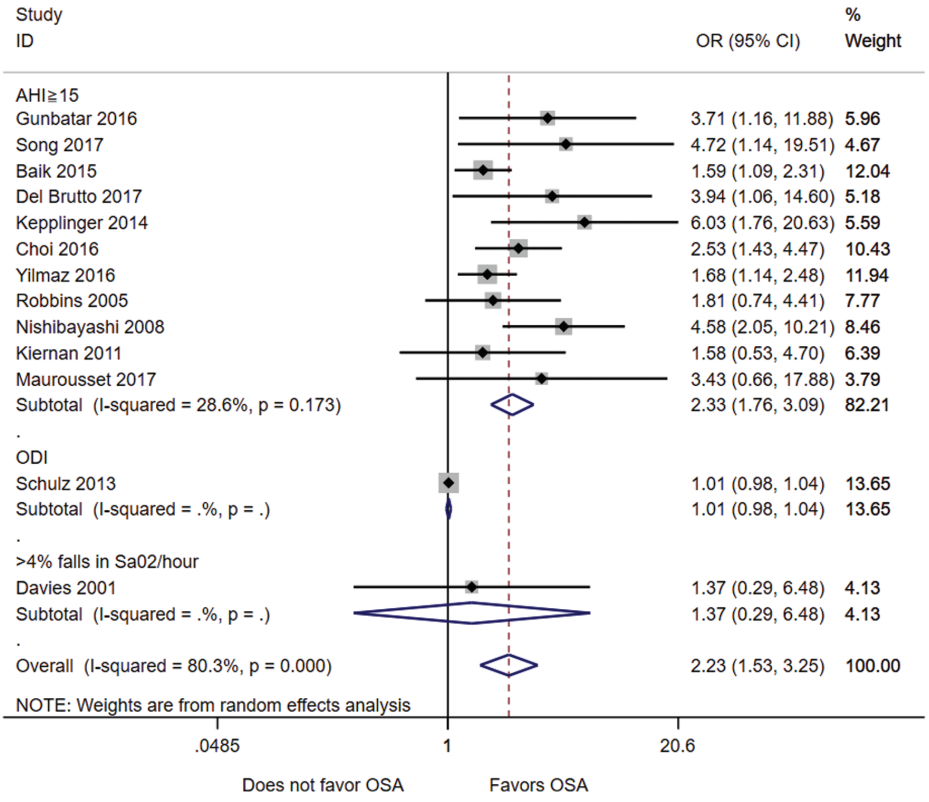

Figure 2. The combined OR and 95% CI of association between OSA and WMHs.

of 15 to more than 30; and severe OSA, AHI of 30 or more. Most of the included studies used an AHI of 15 or more as the cutoff point to investigate the association between OSA and CSVD. All included studies but one (used both CT and MRI) used MRI (0.5–3.0 T) to detect markers of CSVD. The scales or criteria used for judging presences of CSVD varied across studies. For WMH, four studies used the age-related white matter changes (ARWMC) scale [23, 27, 29, 31], two studies used the Fazekas scale [15, 16], four studies used self-defined visualized grade [18, 30, 33, 37], one study used Wahlund score [26], one study mentioned visualized presence [35], and one study was unclear [28]. For SBI, most studies used fluid-filled cavities (3–20 mm) located in the territory of a perforating arteriole. CMBs were low-signal intensity lesions on T2*-weighted gradient-echo images. PVS were punctate or linear hyperintense lesions (<3mm) on T2-weighted images. More details are shown in Supplementary Table 2. Eleven studies reported adjustment for confounders [14–17, 23–27, 29, 32], the most common of which were age and hypertension (Table S3). Quality assessments for each study are shown in Supplementary Tables S4 and S5. For cross-sectional studies using the JBI checklist (eight items), all studies were appraised and accepted if "Yes" was selected for more than five questions. All cohort and case-control studies were rated as seven stars based on NOS criteria, except for one study given six stars.

Association between OSA and WMH

Thirteen studies (n = 4412) investigated the association between moderate to severe OSA and WMH. The meta-analysis showed that moderate to severe OSA was positively associated with WMH (OR = 2.23, 95% CI = 1.53 to 3.25, I^2 = 80.3%) (Figure 2). Meta-analysis of the 11 studies using AHI of 15 or more as the criterion of moderate to severe OSA indicated an association between OSA and WMH (OR = 2.33, 95% CI = 1.76 to 3.09, I^2 = 28.6%). In contrast, this association was not present in data from one study using ODI [29] and another study using more than 4% fall in SaO_2 per hour (Figure 2) [33]. The combined results of six studies (n = 3841) showed no relationship between mild OSA (AHI of 5 to <15) and WMH (OR = 1.14, 95% CI = 0.79 to 1.63, I^2 = 44.7%) (Supplementary Figure S1) [15, 18, 23, 27, 28, 30].

Association between OSA and SBI

For SBI, 12 studies involving 3353 participants were included in the combined analysis. The meta-analysis showed that moderate to severe OSA was positively associated with SBI (OR = 1.54, 95% CI = 1.06 to 2.23, I^2 = 52%; Figure 3), whereas the combined results of five studies (n = 1970) showed no association between mild OSA (AHI of 5 to <15) and SBI (OR = 1.13, 95% CI = 0.56 to 2.26, I^2 = 58.5%; Supplementary Figure 1) [15, 17, 18, 28, 30]. Data from one study using the more than 4% fall in SaO_2 per hour criterion did not indicate an association between OSA and SBI (Figure 3) [33].

Association between OSA and CMBs or PVS

Three studies (n = 342) reported the results of the association between OSA and CMBs. The meta-analysis showed a tendency

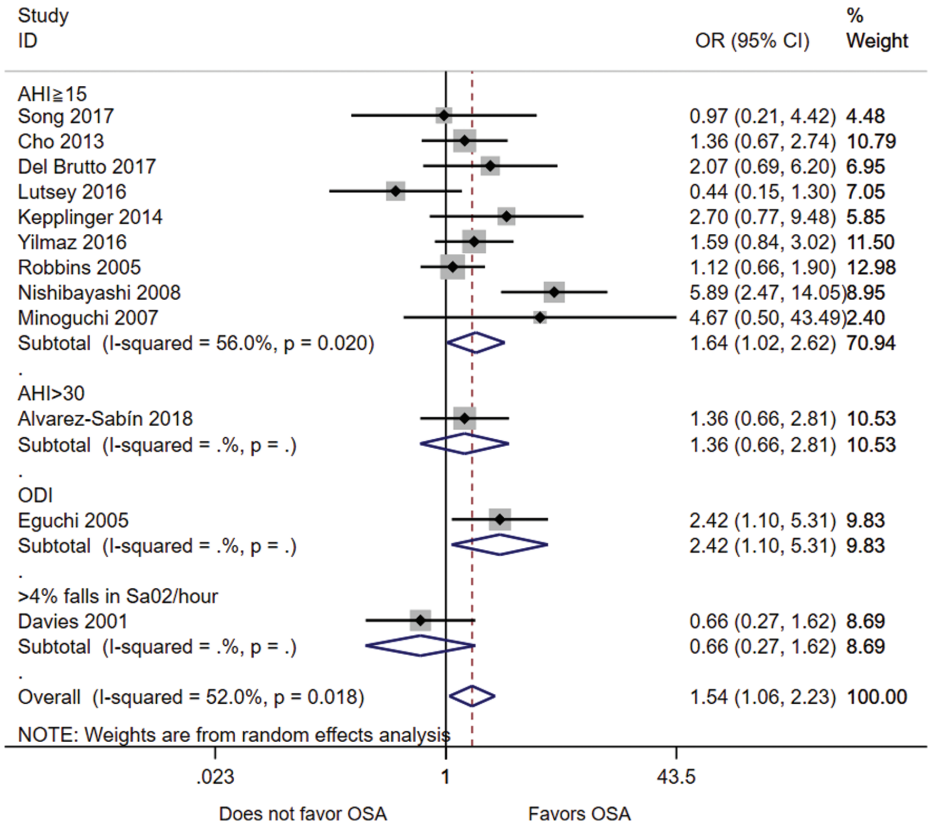

Figure 3. The combined OR and 95% CI of association between OSA and SBI.

toward an association between moderate to severe OSA and CMBs, although it was not statistically significant (OR = 2.17, 95% CI = 0.61 to 7.73, I^2 = 60.2%). Two studies (n = 267) reported the results of OSA and PVS [15, 36], indicating that moderate to severe OSA was not associated with PVS (OR = 1.56, 95%CI = 0.28 to 8.57, I^2 = 69.5%). There was no significant association of mild OSA with CMBs based on one study [15] (OR = 0.39, 95% CI = 0.03 to 4.24) or with PVS based on two studies (OR = 0.98, 95% CI = 0.74 to 1.29, I^2 = 0%) [15, 36].

Subgroup analysis

Subgroup analyses were conducted according to the study design, source of participants, studies with adjusted confounders, different regions, and reported mean or median age. These results are shown in Figure 4. In brief, the association between moderate to severe OSA and WMH was not substantially modified by different subgroups except for different study designs. Ten cross-sectional studies (n = 3423) [15, 16, 23, 26–31, 35] indicated a positive association between moderate to severe OSA and WMH (OR = 2.25, 95% CI = 1.48 to 3.44), as did two case-control studies (n = 146, OR = 2.59, 95% CI = 1.01 to 6.61) [33, 37]. In contrast, one cohort study (n = 843) [18] did not indicate such an association (OR = 1.81, 95% CI = 0.74 to 4.40). An association between OSA and SBI existed only in subgroups of studies performed in Asia and of cross-sectional studies. There was no statistical difference in heterogeneity testing between all subgroups (all p > .05). We did not conduct subgroup analyses with CMBs and PVS because of the low number of relevant studies.

Sensitivity analysis and publication bias

Sensitivity analyses were performed by omitting one study at a time. The OR ranged from 2.04 (95% CI = 1.41 to 2.95) to 2.38 (95% CI = 1.54 to 3.70) for WMH, and from 1.34 (95% CI = 1.00 to 1.79) to 1.67 (95% CI = 1.18 to 2.38) for SBI. The magnitude of the association was not significantly changed by removing one study at a time, indicating that the significance was not attributable to any one study (Figure 5). Publication bias was assessed among studies investigating the association between moderate to severe OSA and WMH or SBI using Begg's and Egger's tests. For WMH, the test results suggested the presence of publication bias (Begg's test, p = .502; Egger's test, p < .001). For SBI, no publication bias was present (Begg's test, p = .537; Egger's test, p = .605). Funnel plots of both WMH and SBI are also displayed in Figure 6 (A and B for WMH; C and D for SBI). Asymmetry in the WMH plot suggests likely publication bias for meta-analyses involving this type of CSVD.

Discussion

In this systematic review and meta-analysis of current studies, we found that moderate to severe OSA was positively associated with the various presences of neuroimaging markers of CSVD, including WMH and SBI but not CMBs or PVS. However, these associations were not significant in participants with mild OSA (AHI of 5 to <15). Severity of sleep apnea may contribute to the pathogenesis of CSVD in patients with OSA.

Accumulating evidence has demonstrated that CSVD abnormalities serve as imaging markers of early cerebral ischemic

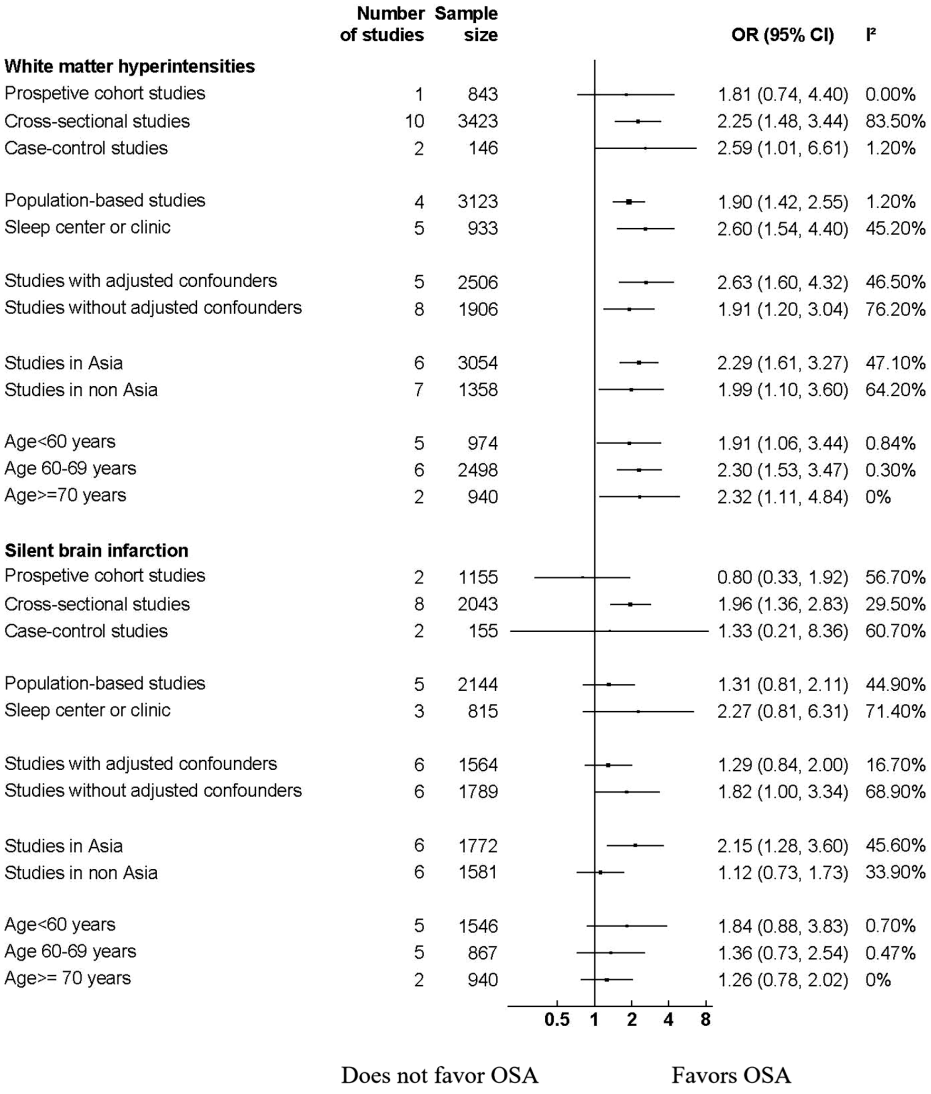

Figure 4. The combined OR and 95% CI of association between OSA and CSVD based on different subgroups.

damage, which can increase the risk of stroke, cognitive disorders, and cardiovascular disease or death [4–6, 38]. In their meta-analysis of population-based studies, Bos et al. indicated that WMH was associated with an increased risk of all-dementia (hazard ratio = 1.39) but that CMBs were not [5]. A recent systematic review of prospective cohort studies showed that any feature of CSVD was associated with the risk of stroke, dementia, and depression, as well as all-cause mortality (hazard ratio = 1.22–2.72) [4]. The most common risk factors for CSVD are age, hypertension, diabetes mellitus, and smoking [2]. However, these traditional risk factors do not fully explain the occurrence of CSVD [9]. Identification of potential risk factors for CSVD may help to reduce the burden of CSVD and the risk of stroke, cognitive impairment, and death.

After gathering the current evidence, we found associations of OSA with WMH and SBI. Recently, a systematic review found that OSA was associated with twofold increased risk of white matter changes (OR = 2.06, 95% CI = 1.52 to 2.80) [39], which was similar to our result (OR = 2.23, 95% CI = 1.53 to 3.25). Our study is more comprehensive than that review because it covers three additional imaging markers of CSVD (SBI, CMBs, and PVS), allowing us to detect an association between moderate to severe sleep apnea and various imaging markers. The complex mechanisms underlying these associations are not well understood. The following potential mechanisms of OSA may increase the risk of CSVD. (1) OSA is associated with sustained high blood pressure and the development of hypertension [40, 41], which might be related to the occurrence of CSVD. (2) Growing data also suggest that OSA often results in systemic inflammation. The activation of an inflammatory reaction may contribute to the development of CSVD. Some studies have shown that blood inflammatory biomarkers, such as C-reactive protein and tumor necrosis factor, are increased in patients with OSA [42, 43]. (3) The effects of nocturnal apnea can increase the hemodynamic changes associated with respiratory events. Abnormal cerebrovascular hemodynamics is reportedly associated with increased intracranial pressure and cerebrovascular endothelial dysfunction, which result in long-term damage to cerebral small vessels

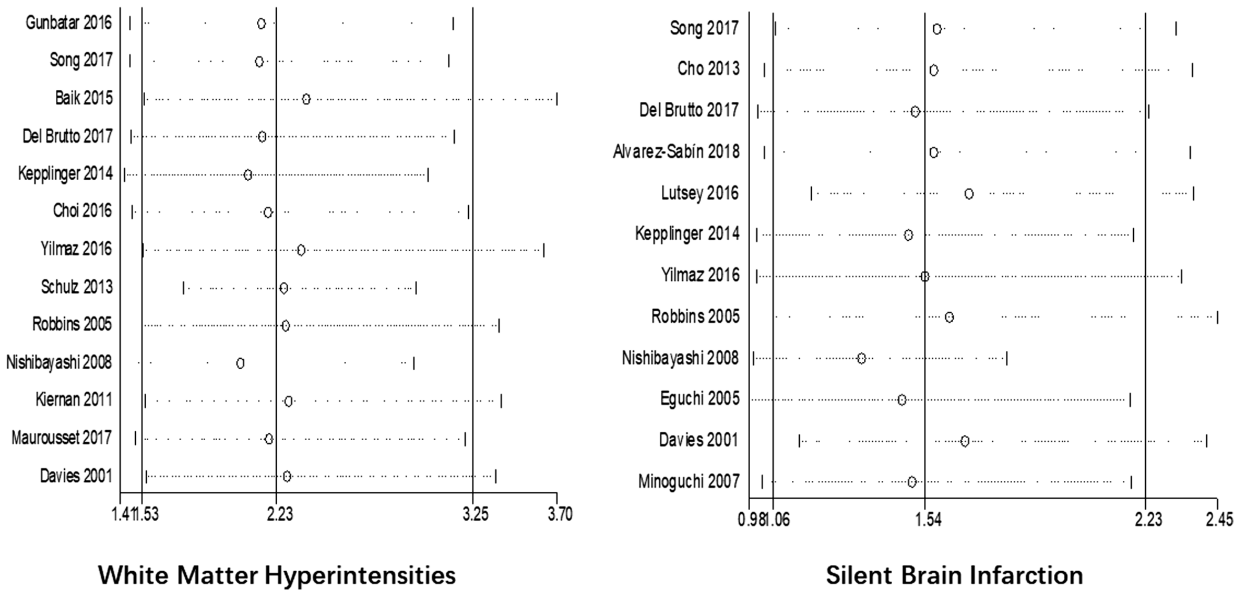

Figure 5. The sensitivity analyses for WMHs and SBI by omitting one study at each turn.

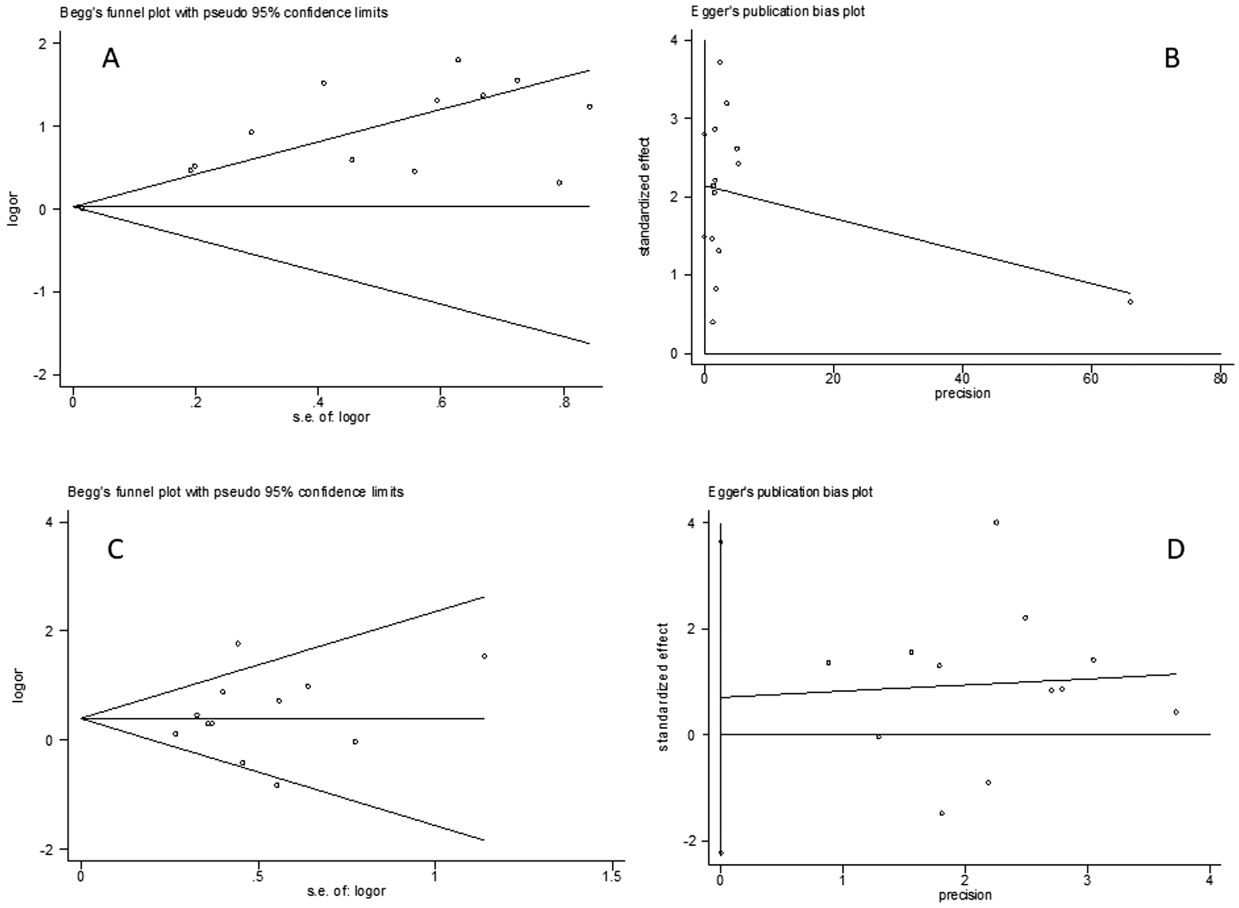

Figure 6. The funnel plot for exploring the publication bias by using the Begg's test and Egger's test.

[44, 45]. (4) A recent meta-analysis showed that moderate to severe OSA was associated with increased arterial stiffness, reduce endothelial function, and chronic inflammation [46]. All these factors are expected to increase the risk of vascular diseases. Therefore, further studies exploring the role of OSA in the pathophysiology of CSVD are required.

The present review has some limitations. First, most of the included studies were cross-sectional in design, so we cannot explore a causal relationship between OSA and CSVD. Long-term follow-up studies are required. In addition, further randomized controlled trials are needed to determine whether the treatment of OSA can prevent the progression of CSVD. Second, few studies investigated the association of OSA with CMBs (three studies) or PVS (two studies), and those studies were underpowered. Whether these imaging markers are related to OSA needs to be further investigated. Third, based on previous studies reporting that OSA and CSVD have common risk factors such as age and hypertension, the relationship between OSA and CSVD may be influenced by these confounders. Although some but not all included studies adjusted for these factors, we cannot exclude that they or unknown variables affected the results. Fourth, conference proceedings and publications written in languages other than English were excluded, which may create publication bias. In fact, publication bias was high in studies investigating WMH, although not in studies investigating SBI. Finally, there are potentially important novel imaging markers that have been recently identified but that we could not analyze, such as cortical microinfarcts and cerebral atrophy. At present, there are large variations in MRI parameters and diagnostic criteria for CSVD, which hampers the interpretation and comparison of data across studies. One publication has recommended neuroimaging standards, including imaging acquisition standards and diagnostic criteria, for research into CSVD [1]. Future cohort studies using these standards should investigate whether there is a bidirectional relationship between OSA and CSVD.

In conclusion, the current evidence suggests that moderate to severe OSA is positively associated with WMH and SBI but not CMBs or PVS. This means that OSA may contribute to the pathogenesis of CSVD. Further larger cohort studies should be prioritized to confirm these findings.

Supplementary Material

Supplementary material is available at *SLEEP* online.

Funding

This work was supported by the National Natural Science Foundation of China (81601012), Key Research and Development Programme, Science and Technology Department of Sichuan Province (2017SZ0007), the National Key Development Plan for Precision Medicine Research (2017YFC0910004), and the 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYGD18009).

Disclosure Statement

All authors report no disclosures for this study.

References

1. Wardlaw JM, *et al.*; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;**12**(8):822–838.
2. Smith EE, *et al.*; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension. Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;**48**(2):e44–e71.
3. Gupta A, *et al*. Silent brain infarction and risk of future stroke: a systematic review and meta-analysis. *Stroke*. 2016;**47**(3):719–725.
4. Rensma SP, *et al*. Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2018;**90**:164–173.
5. Bos D, *et al*. Cerebral small vessel disease and the risk of dementia: a systematic review and meta-analysis of population-based evidence. *Alzheimers Dement*. 2018;**14**(11):1482–1492.
6. Liu Y, *et al*. Cerebral small vessel disease and the risk of Alzheimer's disease: a systematic review. *Ageing Res Rev*. 2018;**47**:41–48.
7. Fanning JP, *et al*. The epidemiology of silent brain infarction: a systematic review of population-based cohorts. *BMC Med*. 2014;**12**:119.
8. Fanning JP, *et al*. Emerging spectra of silent brain infarction. *Stroke*. 2014;**45**(11):3461–3471.
9. Kovács KR, *et al*. Silent brain infarction–a review of recent observations. *Int J Stroke*. 2013;**8**(5):334–347.
10. Drager LF, *et al.*; International Collaboration of Sleep Apnea Cardiovascular Trialists (INCOSACT) Initiative. Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. *Circulation*. 2017;**136**(19):1840–1850.
11. Wang X, *et al*. Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. *Int J Cardiol*. 2013;**169**(3):207–214.
12. Yaggi HK, *et al*. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med*. 2005;**353**(19):2034–2041.
13. Li M, *et al*. Obstructive sleep apnea and risk of stroke: a meta-analysis of prospective studies. *Int J Cardiol*. 2014;**172**(2):466–469.
14. Koo DL, *et al*. Cerebral microbleeds on MRI in patients with obstructive sleep apnea. *J Clin Sleep Med*. 2017;**13**(1):65–72.
15. Song TJ, *et al*. Moderate-to-severe obstructive sleep apnea is associated with cerebral small vessel disease. *Sleep Med*. 2017;**30**:36–42.
16. Del Brutto OH, *et al*. Relationship between obstructive sleep apnea and neuroimaging signatures of cerebral small vessel disease in community-dwelling older adults. The Atahualpa Project. *Sleep Med*. 2017;**37**:10–12.
17. Lutsey PL, *et al*. 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*. 2016;**11**(7):e0158758.
18. Robbins J, *et al*. Associations of sleep-disordered breathing and cerebral changes on MRI. *J Clin Sleep Med*. 2005;**1**(2):159–165.
19. Stroup DF, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;**283**(15):2008–2012.

20. Moher D, *et al.*; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;**6**(7):e1000097.
21. Moola S, Munn Z, Tufanaru C, *et al*. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, eds. *Joanna Briggs Institute Reviewer's Manual*. The Joanna Briggs Institute, 2017. https://reviewersmanual.joannabriggs.org/. Accessed May 8, 2019.
22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;**25**(9):603–605.
23. Baik I, *et al*. Associations of sleep apnea, NRG1 polymorphisms, alcohol consumption, and cerebral white matter hyperintensities: analysis with genome-wide association data. *Sleep*. 2015;**38**(7):1137–1143.
24. Cho ER, *et al*. Obstructive sleep apnea as a risk factor for silent cerebral infarction. *J Sleep Res*. 2013;**22**(4):452–458.
25. Alvarez-Sabín J, *et al*. Obstructive sleep apnea and silent cerebral infarction in hypertensive individuals. *J Sleep Res*. 2018;**27**(2):232–239.
26. Kepplinger J, *et al*. Association of sleep apnea with clinically silent microvascular brain tissue changes in acute cerebral ischemia. *J Neurol*. 2014;**261**(2):343–349.
27. Choi KM, *et al*. Interaction between obstructive sleep apnea and shortened telomere length on brain white matter abnormality. *Sleep*. 2016;**39**(9):1639–1645.
28. Yilmaz Avci A, *et al*. Association between hypoxia parameters with white matter hyperintensity and silent cerebral infarcts on brain magnetic resonance images in patients with obstructive sleep apnea. *J Neurol Sci [Turkish]*. 2016;**33**(3):459–472.
29. Schulz UG, *et al*. Leukoaraiosis on MRI in patients with minimally symptomatic obstructive sleep apnoea. *Cerebrovasc Dis*. 2013;**35**(4):363–369.
30. Nishibayashi M, *et al*. Correlation between severity of obstructive sleep apnea and prevalence of silent cerebrovascular lesions. *J Clin Sleep Med*. 2008;**4**(3):242–247.
31. Kiernan TE, *et al*. Sleep apnea and white matter disease in hypertensive patients: a case series. *Neurologist*. 2011;**17**(5):289–291.
32. Eguchi K, *et al*. Nocturnal hypoxia is associated with silent cerebrovascular disease in a high-risk Japanese community-dwelling population. *Am J Hypertens*. 2005;**18**(11):1489–1495.
33. Davies CW, *et al*. Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. *Sleep*. 2001;**24**(6):715–720.
34. Minoguchi K, *et al*. Silent brain infarction and platelet activation in obstructive sleep apnea. *Am J Respir Crit Care Med*. 2007;**175**(6):612–617.
35. Maurousset A, *et al*. High incidence of obstructive sleep apnea syndrome in patients with late-onset epilepsy. *Neurophysiol Clin*. 2017;**47**(1):55–61.
36. Del Brutto OH, *et al*. Enlarged basal ganglia perivascular spaces and sleep parameters. A population-based study. *Clin Neurol Neurosurg*. 2019;**182**:53–57.
37. Gunbatar H, *et al*. A silent pre-stroke damage: obstructive sleep apnea syndrome. *Int J Clin Exp Med*. 2016;**9**:3481–3488.
38. Norrving B. Evolving concept of small vessel disease through advanced brain imaging. *J Stroke*. 2015;**17**(2):94–100.
39. Ho BL, *et al*. Obstructive sleep apnea and cerebral white matter change: a systematic review and meta-analysis. *J Neurol*. 2018;**265**(7):1643–1653.
40. Hou H, *et al*. Association of obstructive sleep apnea with hypertension: a systematic review and meta-analysis. *J Glob Health*. 2018;**8**(1):010405.
41. Lombardi C, *et al*. Systemic hypertension in obstructive sleep apnea. *J Thorac Dis*. 2018;**10**(Suppl 34):S4231–4243.
42. van Dijk EJ, *et al*. C-reactive protein and cerebral small-vessel disease: the Rotterdam Scan Study. *Circulation*. 2005;**112**(6):900–905.
43. Gozal D, *et al*. Sleep measures and morning plasma TNF-alpha levels in children with sleep-disordered breathing. *Sleep*. 2010;**33**(3):319–325.
44. Jennum P, *et al*. Intracranial pressure and obstructive sleep apnea. *Chest*. 1989;**95**(2):279–283.
45. Klingelhöfer J, *et al*. Assessment of intracranial hemodynamics in sleep apnea syndrome. *Stroke*. 1992;**23**(10):1427–1433.
46. Wang J, *et al*. Impact of obstructive sleep apnea syndrome on endothelial function, arterial stiffening, and serum inflammatory markers: an updated meta-analysis and meta regression of 18 studies. *J Am Heart Assoc*. 2015;**13**(4):pii:e002454.