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Moderate-to-severe obstructive sleep apnea is associated with cerebral small vessel disease

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Highlights

- The association of small vessel diseases with obstructive sleep apnea has been not solved.
- Obstructive sleep apnea was associated with high-grade white matter hyperintensities.
- Obstructive sleep apnea was marginally related with cerebral microbleeds.
- Obstructive sleep apnea was marginally related with perivascular spaces.
- Total small vessel disease score was positively associated with apnea-hypopnea index.

Abstract

Background: Cerebral small vessel disease (SVD) is associated with increased risk of cerebral infarction and hemorrhage. Obstructive sleep apnea (OSA) is known to increase the risk of cerebrovascular disease. This study aimed to investigate the association between cerebral SVD and severity of OSA.

Methods: A total of 170 patients were included from the patient registry at the present Sleep Center; these patients underwent both magnetic resonance imaging (MRI) of the brain and polysomnography (PSG) for suspected OSA. The presence and burden of white matter hyperintensities (WMHs), asymptomatic lacunar infarctions (ALIs), cerebral microbleeds (CMBs), and perivascular spaces (PVSs) were determined by MRI, and their relationships with the apnea-hypopnea index (AHI), as determined by PSG, were investigated.

Results: Among the 170 patients, 25 (14.7%) had high-grade WMHs, 21 (12.4%) had ALIs, 21 (12.4%) had CMBs, and 34 (20.0%) had high-grade PVSs. In the multivariable analysis, after adjusting for factors including age, sex, and other variables for which $p<0.1$ in
univariable analysis (hypertension, diabetes mellitus, previous stroke, minimal SaO₂ and arousal index), moderate-to-severe OSA was associated with high-grade WMHs (odds ratio (OR) 4.72; 95% confidence interval (CI) 1.14-19.47), CMBs (OR 3.47; 95% CI 0.89-15.18), or high-grade PVSs (OR 3.64; 95% CI 1.02-13.01), but not with ALIs. The total SVD score was independently associated with increased AHI \( (p=0.017) \), particularly in patients with moderate-to-severe OSA \( (\beta \text{ (standard error)}=0.448 \text{ (0.204)}, p=0.030) \).

**Conclusion:** Moderate-to-severe OSA is positively associated with multiple indicators of cerebral SVD, including WMHs, CMBs, and PVSs.

**Keywords:**

Obstructive sleep apnea

Small vessel disease

Apnea-hypopnea index
Introduction
Cerebral small vessel disease (SVD) is characterized by perforation of small arterioles, with pathology that presents as abnormal high/low signal intensities on brain magnetic resonance imaging (MRI), including: white matter hyperintensities (WMHs), asymptomatic lacunar infarctions (ALIs), cerebral microbleeds (CMBs), and perivascular spaces (PVSs) [1]. These indicators of SVD are closely related to the risk of symptomatic cerebral ischemia and/or hemorrhage, post stroke dementia, vascular cognitive impairment, and recurrent and future stroke [2, 3].

Meanwhile, obstructive sleep apnea (OSA) has been reported as one of the risk factors for vascular diseases, including stroke [4]. In previous studies of patients with suspected OSA from a community-dwelling population, the presence of nocturnal hypoxia and moderate-to-severe OSA was associated with WMHs and ALIs [5, 6]. In contrast, a case-control study that compared patients with OSA and normal, matched control subjects showed no significant correlation between OSA and SVD (WMHs and ALIs) [7]. Moreover, although each SVD can have a somewhat different impact on clinical presentation (CMBs for cerebral hemorrhage [8] and WMHs or ALIs for cerebral ischemia [9]), whether OSA is an independent risk factor for the presence of CMBs or PVSs, and the total burden of cerebral SVD have not yet been determined.

The objective of the present study was to investigate the association between the presence and burden of each indicator of SVD with the apnea-hypopnea index (AHI), which represents the severity of sleep apnea, in patients with OSA.
Materials and Methods

Subjects

A total of 185 patients were identified who were referred to the Sleep Center of the Ewha Medical Center for suspected OSA between March 2009 and July 2014. All patients included in the study had one or more OSA-related symptom, such as: witnessed loud snoring between apneas, witnessed episodes of gasping for air, choking, sleep fragmentation/insomnia, and non-refreshing sleep [10]. Patients underwent overnight polysomnography (PSG) and brain MRI within 60 days before (n=160) or after (n=25) PSG. Thirteen patients were excluded who had no available gradient recalled echo (GRE) images, and two patients were excluded due to poor image quality. Therefore, a total of 170 patients were included in this study.

The main indications for performing brain MRI were: headache and dizziness (n=67, 39.4%); rapid eye movement (REM) sleep behavior disorder (n=22, 12.9%); patient’s request (n=17, 10.0%); complaints of cognitive decline (n=15, 8.8%); insomnia with sleep fragmentation (n=13, 7.6%); loss of consciousness history (n=10, 5.9%); stroke or transient ischemic attack (n=9, 5.3%); suspected restless leg syndrome or periodic limb movement (n=9, 5.3%); excessive daytime sleepiness (n=6, 3.5%); and narcolepsy (n=2, 1.2%). All of the PSG and MRI data from the included patients were acquired before the initiation of OSA treatments (including continuous positive airway pressure therapy, CPAP).

The hospital Institutional Review Board approved the study, and the patients’ informed consent was waived because of the study’s retrospective and observational nature.
MRI protocol, definition of small vessel diseases and vascular stenosis

Each patient underwent a brain MRI within a median of 11 days (interquartile range: 2-41 days) from the day of PSG monitoring. The detailed protocol of the brain MRI had previously been described [11]. All MRI examinations were performed with a 3T scanner (Philips Achieva v2.6, Best, The Netherlands). Brain MRI image slices were acquired parallel to the orbitomeatal line using the following parameters: for fluid-attenuated inversion recovery (FLAIR), time repetition (TR)/time echo (TE) = 12000/120 ms, pixel spacing = 0.449 mm/0.449 mm, field of view (FOV) = 183 × 230 mm, and slice thickness = 5 mm; for T2-weighted images, TR/TE = 15000/90 ms, pixel spacing = 0.240 mm/0.240 mm, FOV = 176 × 220 mm, and slice thickness = 5 mm; and for GRE, TR/TE = 571/21.9 ms, pixel spacing = 0.449 mm/0.449 mm, FOV = 145 × 250 mm, and slice thickness = 5 mm [12].

The extent of white matter changes was determined on the FLAIR images for the periventricular white matter (PVWM) or deep white matter (DWM), according to Fazekas scale [13]. Fazekas scores of ≥2 in periventricular white matter hyperintensities (PWMHs) and/or ≥2 in deep white matter hyperintensities (DWMHs) were considered to indicate high-grade white matter hyperintensities (HWMHs). An ALI was defined as a 3-15 mm lesion showing as hyperintense on axial T2-weighted images and hypointense on axial T1-weighted images in a subject lacking a relevant history of symptoms or signs [8]. The CMBs were identified as punctate hypointense lesions <10 mm in size on GRE images [14]. The PVSs were defined as punctate or linear hyperintense lesions on T2-weighted images in the basal ganglia and <3 mm in size [12]. Subjects were coded with the following grades: 0 = no PVSs,
1≤ 10 PVSs, 2 = 11-20 PVSs, 3 = 21-40 PVSs, and 4 ≥40 PVSs. High-grade perivascular space (HPVS) subjects were defined as those of grade 2-4, based on PVSs in the basal ganglia or centrum ovale [15] (Fig. 2). Two neurologists (TJS and JHP), who were blinded to the patients’ clinical information, independently investigated the presence of HWMHs, ALIs, CMBs and HPVSs. The kappa values for the inter-observer agreement on the presence of HWMHs, ALIs, CMBs, and HPVSs were 0.89, 0.91, 0.83, and 0.84, respectively. Consensus was reached in cases of discrepancy for the detection of SVD. The total SVD (0-4) score was calculated by the summation of one point per category for the existence of CMBs, high-grade WMHs, high-grade PVSs, and ALIs, as outlined previously [15].

Polysomnography

Polysomnography (PSG) was performed as previously described [16]. The duration of OSA symptoms was defined as the time interval from the date of the first OSA-related symptom to the date that PSG was performed. Overnight PSG was performed with a comprehensive device (TWin® PSG Clinical Software; Grass Technologies, Warwick, RI, USA) at the sleep laboratory of the Ewha Sleep Center. Apneas were defined as events when airflow was reduced to ≥90% of the baseline values for at least 10 seconds, and apneas were further classified as obstructive type if respiratory efforts were noted on either the chest or the abdominal belt channel, or as central type if no respiratory effort was noted. Hypopneas were defined as events with a ≥30% reduction of airflow for at least 10 seconds and accompanied by at least a 3% drop in oxygen saturation (SaO₂) or an arousal [17, 18]. The arousal index was defined as the number of arousals per hour. The AHI was calculated by averaging the total number of obstructive apneas and hypopneas per hour of sleep, and OSA severity was
determined based on the AHI: no OSA (AHI <5), mild OSA (5≤ AHI <15), and moderate-to-severe OSA (AHI ≥15) [16].

Risk factors

The definitions for having a history of risk factors, including hypertension, diabetes mellitus, hyperlipidemia, presence of coronary artery disease, previous stroke, alcohol intake and current smoking, are described in the supplemental methods.

Statistical analyses

Statistical analyses were performed using the Windows SPSS software package (version 21.0, Chicago, IL, USA). Continuous variables were expressed as means ± standard deviations (SD), and categorical variables were expressed as frequencies and percentages. Differences between the reference and case (presence of cerebral SVD) groups regarding demographic characteristics and presence of vascular risk factors were determined by Fisher’s exact test, the Chi-squared test, the Mann-Whitney U test, independent t-tests or one-way analysis of variance with Bonferroni post-hoc analysis. Clinical variables such as age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, coronary artery disease, previous history of stroke, alcohol intake, smoking, body mass index (BMI), minimum O₂ saturation, snoring index, arousal index, central apnea index, and AHI, were compared using univariable binary logistic regression analysis with the existence of each SVD indicator as a dependent variable. The relationship between the existence of each SVD indicator and the AHI was investigated by multivariable analysis after adjusting for age and sex, and variables with p<0.1 in the univariable analyses (hypertension, diabetes mellitus, previous stroke, minimal SaO₂, and
arousal index), with patients in the ‘no OSA (AHI <5)’ group serving as a reference. The association between the total SVD score and the AHI was evaluated using Spearman correlation analysis and linear regression analysis. Because there were more than seven variance inflation factors among the SVD indicators, each indicator and the total SVD score were analyzed separately in multivariable analyses. A two-tailed p-value <0.05 was considered statistically significant.

Results

Demographic data and presence of small vessel disease

The demographic data of the enrolled patients and the comparative analysis of the presence of HWMHs, ALIs, CMBs, and HPVSs are shown in Table 1. Patients were an average of 58±13 years old, and 57.1% (97/170) were male. The mean AHI was 20.2±21.7 and that of the minimum SaO2 level was 83.5±8.6. The distribution of patients in terms of the severity of OSA was as follows: 55 (32.4%) had no OSA, 40 (23.5%) had mild OSA, and 75 (44.1%) had moderate-to-severe OSA. Other sleep disorders accompanying OSA were also noted: restless leg syndrome (n=18, 10.6%); periodic limb movement (n=18, 10.6%); REM sleep behavior disorder (n=30, 17.6%); and narcolepsy (n=3, 1.8%). Patients with older age, a history of hypertension, diabetes mellitus, coronary artery disease, previous stroke, and increased BMI were more frequently noted to have mild or moderate-to-severe OSA rather than having no OSA (Supplemental Table 1).
Among the 170 patients, 25 (14.7%) had HWMHs, 21 (12.4%) had ALIs, 21 (12.4%) had CMBs, and 34 (20.0%) had HPVs. The mean SVD score was 0.6±1.0. Patients with SVD indicators were older and more likely to have multiple indicators (HWMHs, ALIs, CMBs, and HPVSs). There were no associations between the mean duration of OSA symptoms and the presence of each SVD indicator. In contrast, the mean arousal index was significantly higher in patients with HWMHs (23.8±13.6 vs 33.9±22.7, p=0.015) and HPVSs (16.4±19.8 vs 35.0±23.0, p=0.001) than in those without (Table 1). There were no associations between the frequency of other sleep disorders accompanying OSA and the presence of each SVD indicator (Supplemental Table 2). In terms of the AHI, relatively higher AHI values were noted in patients with HWMHCs, ALIs, and HPVSs, but not in those with CMBs.

Considering the severity of the OSA, moderate-to-severe OSA was frequently noted in patients with HWMHCs, CMBs, and HPVS, but moderate-to-severe OSA was not associated with ALIs (Table 1).

Association of AHI with cerebral SVD

The severities of periventricular (ρ=0.265, p<0.001) and deep (ρ=0.200, p<0.001) WMHs were positively correlated with the AHI, but not with the number of ALIs (ρ=0.130, p=0.102). The burden of CMBs (ρ=0.201, p=0.008) and PVSs (ρ=0.338, p=0.004) also displayed a positive relationship with the AHI. Furthermore, the total SVD score was associated with the AHI (ρ=0.327, p<0.001) (Table 2). In the multivariable analysis, increased AHI was independently related to the presence of HWMHs (odds ratio (OR) 1.03, 95% confidence interval (CI) 1.01-1.06) and HPVSs (OR 1.02, 95% CI 1.00-1.04).

Considering the severity of OSA, only moderate-to-severe OSA was significantly associated with the presence of HWMHs (OR 4.72, 95% CI 1.14-19.47) and HPVSs (OR 3.64, 95% CI
1.02-13.01). Moreover, this severity level had a marginally significant association with the existence of CMBs (OR 3.47, 95% CI 0.89-15.18), but not with that of ALIs (OR 0.96, 95% CI 0.21-4.36) (Table 3). In addition, the total SVD score was independently associated with increased AHI (β=0.010, standard error = 0.004, p=0.017). In particular, the total SVD score was related with moderate-to-severe OSA (β=0.448, standard error = 0.204, p=0.030, p for trend = 0.001) (Table 4) (Fig. 1).

**Discussion**

The results include new and additional findings for the correlation of OSA with cerebral SVD. Moderate-to-severe OSA (AHI ≥15) may be associated with the hemorrhagic damage (mainly CMBs) as well as ischemic change (HWMHs and HPVSs) indicators of cerebral SVD. Because CMBs are image biomarkers for the occurrence of future intracerebral hemorrhage [2, 8], and HWMHs and HPVSs are putative markers for early cerebral ischemic damage or increased blood-brain barrier permeability [1, 19], the present cross-sectional study supports the findings of a previous meta-analysis that suggested that OSA was associated with a significantly increased risk of fatal or non-fatal stroke [20]. Moreover, in the present study, higher AHI correlated with total SVD score. Because the total SVD score reflects the burden of overall SVD indicators, it may be concluded that moderate-to-severe OSA is closely related to cerebral SVD in general. In previous studies, the relationship between OSA and WMHs remained inconclusive. In one study of patients who visited a sleep clinic, those with moderate-to-severe OSA had a higher prevalence of WMHs [6]; however,
another cross-sectional study did not reproduce this association [21]. This inconsistency was also noted in studies of the general population. In the Sleep Health Heart Study, the progression of WMHs was related with central sleep apnea, but not with OSA [22]. However, in a study of a middle-aged and older Asian population, OSA was a risk factor for cerebral WMHs [16]. The present results are consistent with these previous findings and provide additional information regarding the association of OSA with CMBs and PVSs.

In the present study, although the AHI was relatively higher in patients with ALIs compared to those without, there was no significant relationship between the AHI and ALIs in the multivariable analysis. The results were similar to those of a previous case control study [7] that observed no significant association between the presence of OSA and ALIs. However, another study showed opposing results [23]. One possible explanation for the weak relationship between OSA and ALIs is that it may be influenced by other stronger intervening variables such as age or hypertension. Furthermore, the development of ALIs could be different from that of other cerebral SVD indicators, in that ALIs could arise from microembolic infarction [24]. Furthermore, the relatively small number of patients in the present study could cause statistical bias. Therefore, further investigation of the relationship between the AHI and ALIs is needed.

Based on previous studies reporting that OSA and cerebral SVD have common risk factors [25-28], the present study looked for possible confounding variables, such as hypertension and diabetes mellitus, by using univariable analysis. After controlling for these confounding variables by multivariable analysis, there was still a significant association between OSA and cerebral SVD indicators. Moreover, fluctuation of cerebral blood flow induced by alteration of blood pressure occurring in OSA could cause cerebral SVD. Repeated hypoxemia and
hypercapnia during sleep apnea activate sympathetic vasoconstriction and this vasoconstriction induces the elevation of blood pressure followed by an abrupt decline [29]. A previous study showed that a fluctuation or variability in blood pressure was related to the presence of cerebral SVD [30]. Therefore, these fluctuations could cause shearing forces to the cerebral vasculature, and these shearing forces could injure arterioles leading to cerebral SVD. In addition, the activation of an inflammatory reaction or increased arterial stiffness induced by intermittent hypoxemia could contribute to the development of cerebral SVD. Indeed, increases in blood biomarkers representing systemic inflammation or hypercoagulability such as C-reactive protein [31] and tumor necrosis factor [32] have been noted in patients with OSA. Considering arterial stiffness, a recent meta-analysis showed that moderate-to-severe OSA was independently associated with increased carotid femoral pulse wave velocity, which represents arterial stiffness [33]. Because cerebral SVD indicators are related with these systemic inflammation markers [34, 35] and increased arterial stiffness [36], the observation of a close association between increased AHI and cerebral SVD is plausible.

It is acknowledged that there were some limitations to this study. First, the study retrospectively included a small sample size of patients who visited the present hospital, and completed brain MRI and PSG. This retrospective design and small sample size introduced the possibility of sampling bias and may have limited power for generalization. Therefore, marginal significance for association between the severity of OSA and CMBs has to be carefully interpreted. Second, the lack of an association between the duration of OSA symptoms and SVD could be caused by recall bias of the patient’s cohabiter or external intervening factors. Therefore, there is a need for a further validation study and caution
should be exercised in generalizing the finding of association between OSA and cerebral SVD.

Conclusion

In conclusion, the results confirmed that moderate-to-severe OSA was associated with cerebral SVD in patients with suspected OSA who were also sent for MRI. Further studies are needed to determine whether treatment of OSA would prevent progression of SVD.
Acknowledgments

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Conflicts of interest: None.

References

Figure legend

**Fig. 1.** Distribution of total small vessel disease scores according to severity of obstructive sleep apnea ($p$ for trend =0.001).

AHI, apnea hypopnea index; SVD, small vessel disease

$x$-axis, severity of OSA; $y$-axis number (%) of each total SVD score

**Fig. 2.** (A) High-grade white matter changes (white arrowhead); (B) Asymptomatic lacunar infarction (white arrowhead); (C) Cerebral microbleeds (white arrowhead); and (D) High-grade perivascular spaces (white arrowhead).

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[Comment [JM9]: Please check figure numbers as per my comments in the main text]
Fig. 1

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<tr>
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<th>No (AHI &lt; 5)</th>
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<td>3 (7.5%)</td>
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<td>4 (10.0%)</td>
<td>4 (5.3%)</td>
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<td>33 (82.5%)</td>
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<td>49 (89.2%)</td>
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<td>39 (52.0%)</td>
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Comment [JM11]: I was unable to edit this. Please close up p = 0.001 as in main text, and <5, ≥15.
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<th>Demographic data</th>
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<th>Age (years)</th>
<th>OSA symptom duration (months)</th>
<th>Risk factors</th>
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<tr>
<td>Total 170 (100)</td>
<td>HWMHs (–) 145 (85.3)</td>
<td>HWMHs (+) 25 (14.7)</td>
<td>HWMHs 149 (87.6)</td>
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<td>ALIs (+) 21 (12.4)</td>
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<td>CMBs (–) 149 (87.6)</td>
<td>CMBs (+) 21 (12.4)</td>
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<td>HPVSs (–) 136 (80.0)</td>
<td>HPVSs (+) 34 (20.0)</td>
<td>Total 136 (80.0)</td>
<td>Total 64±10</td>
<td>Total 17 (11.4)</td>
</tr>
<tr>
<td>Hypertension 74 (43.5)</td>
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<td>Total 5 (13.1)</td>
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</tr>
<tr>
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<tr>
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<td>Total 3 (12.0)</td>
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<td>Total 6 (17.6)</td>
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<td>Total 14 (41.2)</td>
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Table 1. Comparison of demographic and clinical data according to the presence of cerebral small vessel disease.
<table>
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<tr>
<th>Category</th>
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<th>Minimum SaO₂</th>
<th>1.8 ±1.0</th>
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<th>1.7 ±2.6</th>
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<th>1.5 ±2.5</th>
<th>1.8 ±3.0</th>
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<td>Minimum SaO₂</td>
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<td>Snoring index</td>
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<td>2.2±3.1</td>
<td>1.5±2.5</td>
<td>1.8±3.0</td>
<td>1.4±2.5</td>
<td>1.9±2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arousal index</td>
<td>24.6±16.6</td>
<td>23.8±13.6</td>
<td>33.9±22.7</td>
<td>23.5±15.4</td>
<td>33.0±21.7</td>
<td>23.7±15.5</td>
<td>31.1±22.2</td>
<td>21.6±14.2</td>
<td>36.6±20.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central apnea index</td>
<td>0.5±2.2</td>
<td>0.5±2.2</td>
<td>1.0±2.2</td>
<td>0.5±2.2</td>
<td>0.9±1.9</td>
<td>0.5±2.0</td>
<td>1.4±3.1</td>
<td>0.4±2.1</td>
<td>1.1±2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
<td>20.2±21.7</td>
<td>22.9±15.0</td>
<td>34.6±21.6</td>
<td>19.2±21.3</td>
<td>27.2±24.2</td>
<td>19.6±21.7</td>
<td>24.5±22.4</td>
<td>16.4±19.8</td>
<td>35.0±23.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of OSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (AHI &lt;5)</td>
<td>55 (32.4)</td>
<td>52 (35.9)</td>
<td>3 (12.0)</td>
<td>51 (34.2)</td>
<td>19 (9.0)</td>
<td>52 (34.9)</td>
<td>3 (14.3)</td>
<td>51 (37.5)</td>
<td>4 (11.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (5 ≤ AHI &lt;15)</td>
<td>40 (23.5)</td>
<td>39 (26.9)</td>
<td>1 (4.0)</td>
<td>36 (24.2)</td>
<td>19 (9.0)</td>
<td>39 (26.2)</td>
<td>1 (4.0)</td>
<td>36 (26.5)</td>
<td>4 (11.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate-to-severe (AHI ≥15)</td>
<td>75 (44.1)</td>
<td>54 (37.2)</td>
<td>21 (84.0)</td>
<td>62 (41.6)</td>
<td>13 (61.9)</td>
<td>58 (38.9)</td>
<td>17 (81.0)</td>
<td>49 (36.0)</td>
<td>26 (76.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are number (%) or means±standard deviation.

AHI, apnea-hypopnea index; ALIs, asymptomatic lacunar infarctions; BMI, body mass index; CMBs, cerebral microbleeds; DWMHs, deep white matter hyperintensities; HPVSs, high-grade perivascular spaces; HWMHs, high-grade white matter hyperintensities; OSA, obstructive sleep apnea; PVWMHs, periventricular white matter hyperintensities; SVDs, small vessel diseases; WMHs, white matter hyperintensities.
* p<0.05 by Fisher’s exact or Chi-squared test (comparing severity of OSA with cerebral SVDs) for categorical variables, independent t-tests for continuous variables
Table 2. Correlation between burden of cerebral small vessel diseases and the severity of obstructive sleep apnea.

<table>
<thead>
<tr>
<th>Burden of cerebral small vessel diseases</th>
<th>Spearman’s rho with apnea-hypopnea index</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periventricular white matter hyperintensities&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.265</td>
<td>0.001**</td>
</tr>
<tr>
<td>Deep white matter hyperintensities&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.200</td>
<td>0.001**</td>
</tr>
<tr>
<td>Asymptomatic lacunar infarction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.130</td>
<td>0.102</td>
</tr>
<tr>
<td>Cerebral microbleeds&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.201</td>
<td>0.008**</td>
</tr>
<tr>
<td>Perivascular spaces&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.338</td>
<td>0.004**</td>
</tr>
<tr>
<td>Total small vessel disease score</td>
<td>0.327</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

<sup>a</sup> according to Fazekas grading
<sup>b, c, d</sup> total number of each small vessel diseases

*<sup>p</sup><0.05

**<sup>p</sup><0.001

Comment [JM13]: There is no p-value with one * in this table, please check.
Table 3. Association between the severity of OSA and the presence of small vessel pathologies.

<table>
<thead>
<tr>
<th>Severity of OSA*</th>
<th>High-grade white matter hyperintensities</th>
<th>Asymptomatic lacunar infarctions</th>
<th>Cerebral microbleeds</th>
<th>High-grade perivascular space</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (AHI &lt;5)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Mild (5 ≤ AHI &lt;15)</td>
<td>0.27 (0.02-3.37)</td>
<td>1.03 (0.21-4.90)</td>
<td>0.966</td>
<td>1.22 (0.26-5.68)</td>
</tr>
<tr>
<td>Moderate-to-severe (AHI ≥15)</td>
<td>4.72 (1.14-19.47)</td>
<td>0.967 (0.21-4.36)</td>
<td>3.47 (0.79-15.18)</td>
<td>3.64 (1.02 – 13.01)</td>
</tr>
</tbody>
</table>

Values are odds ratio (OR) and 95% confidence interval (CI)

AHIL, apnea-hypopnea index; OSA, obstructive sleep apnea

*adjusting age, sex and variables with p<0.1 in univariable analyses (hypertension, diabetes mellitus, previous stroke, minimal SaO₂ and arousal index)
Table 4. Relationship between total small vessel disease score and apnea-hypopnea index

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (Standard error)</td>
<td>p</td>
<td>β (Standard error)</td>
<td>p</td>
</tr>
<tr>
<td>AHI per 1 increase</td>
<td>0.016 (0.004)</td>
<td>0.001</td>
<td>0.010 (0.004)</td>
<td>0.017</td>
</tr>
<tr>
<td>Severity of OSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (AHI &lt;5)</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Mild (5 ≤ AHI &lt;15)</td>
<td>-0.005 (0.213)</td>
<td>0.983</td>
<td>-0.063 (0.212)</td>
<td>0.767</td>
</tr>
<tr>
<td>Moderate-to-severe (AHI ≥15)</td>
<td>0.772 (0.182)</td>
<td>0.001</td>
<td>0.448 (0.204)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

<sup>a</sup>Values are derived from linear regression analysis

AHI, apnea-hypopnea index; OSA, obstructive sleep apnea

<sup>a</sup>adjusting age, sex and variables with p<0.1 in univariable analyses (hypertension, diabetes mellitus, previous stroke, minimal SaO<sub>2</sub> and arousal index)