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# Lighter sleep is associated with higher enlarged perivascular spaces burden in middle-aged and elderly individuals

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## Abstract

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**Background:** While healthy sleep is suggested to promote glymphatic clearance in the brain, poorer sleep may be associated with higher enlarged perivascular spaces (ePVS) burden, potentially representing impaired perivascular drainage. This study aims to evaluate the association between ePVS burden and polysomnographic sleep characteristics in a large community-based sample.

**Methods:** 552 dementia and stroke-free Framingham Heart Study participants (age: 58.6 ± 8.9 years; 50.4% men) underwent a full-night in-home polysomnography. Three years later on average, participants underwent brain MRI. ePVS were rated in the basal ganglia and centrum semiovale, and dichotomized as low burden (<20 counts, grades 1 and 2) or high burden (>20 counts, grades 3 and 4). Logistic regression analyses relating sleep variables to subsequent ePVS burden were used, adjusted for age, sex, time interval between polysomnography and MRI, *ApoE ε4* allele carrier status, hypertension, and smoking.

**Results:** Longer N1 sleep and shorter N3 sleep duration were associated with higher ePVS burden in the centrum semiovale. When stratifying these associations by subpopulations, longer N1 sleep duration was observed especially in older individuals and hypertensive participants. Associations between ePVS burden and other sleep characteristics such as total sleep time and REM sleep duration varied according to *ApoE ε4* allele carrier status.

**Conclusions:** Lighter sleep, as characterized by longer N1 sleep and shorter slow-wave sleep, is associated with higher ePVS burden. These findings suggest that sleep architecture may be involved in glymphatic clearance and cerebral small vessel disease, which could be an important biological link between sleep and dementia risk.

### Keywords

slow-wave sleep; REM sleep; obstructive sleep apnea; interstitial fluid; cerebrovascular diseases; glymphatic

## 1. Introduction

Enlarged perivascular spaces (ePVS) on brain MRI are novel markers of small vessel disease (SVD) [1] and are associated with increased stroke and dementia risk [2, 3]. Whereas normal PVS are thought to contribute to adequate fluid drainage, ePVS could be caused by blood-brain barrier dysfunctions, accumulated debris and waste products, and inflammation, all potentially leading to further blockage and impaired clearance [1]. In fact, in patients with SVD, higher ePVS burden is associated with poorer glymphatic function as measured with a diffusion imaging marker.[4]

Sleep disturbances are increasingly recognized as risk factors for stroke and dementia [5–7]. One of the potential mechanisms linking sleep to SVD and cognitive outcomes is its recently discovered role in glymphatic clearance [8]. Indeed, increased interstitial spaces during sleep contributes to the removal of metabolic waste products via perivascular pathways. Enhanced glymphatic clearance has been associated especially with deeper sleep, i.e., slow-wave sleep (SWS), with increased cerebrospinal fluid flow time-locked with slow oscillations [9]. Therefore, poorer sleep lacking in SWS might be associated with disturbed fluid exchanges between interstitial spaces, PVS, and cerebrospinal fluid leading to poorer clearance of

waste products from the brain. Therefore, poorer waste products clearance following sleep disturbances and shorter SWS could lead to ePVS.

Self-reported sleep disturbances have previously been linked to higher ePVS burden [10, 11]. Additionally, a few previous studies have shown that higher ePVS burden was associated with objectively assessed sleep parameters indicating disrupted sleep (e.g., shorter sleep efficiency and sleep duration, shorter SWS and rapid-eye movement [REM] sleep, sleep fragmentation), and the presence of sleep disorders (e.g., as insomnia, obstructive sleep apnea, periodic limb movements during sleep) [12–20]. However, many of these studies were performed in small clinical samples with varying results, and thus, questions remain about how sleep architecture is associated with ePVS burden in the community and in specific at-risk subpopulations. Understanding the association between sleep architecture with ePVS burden will contribute to clarify the association between sleep disturbances and glymphatic function and SVD. In this study, we investigated whether sleep architecture measured with polysomnography (PSG), especially SWS and other sleep stages, were associated with subsequent ePVS burden in a sample of over 550 participants from the Framingham Heart Study (FHS). Additionally, we explored these relationships in stratified subpopulations according to specific stroke and dementia risk factors, i.e., *ApoE ε4* allele carrier status, age, and hypertension.

## 2. Material and methods

### 2.1 Sample

In the community-based FHS Offspring cohort [21], 699 out of 5124 participants were enrolled within the Sleep Heart Health Study (SHHS) using PSG close to their sixth clinic examination between 1995 and 1998. Participants have been invited to undergo brain MRI after each clinic examination, starting with their seventh examination (1998–2001). Participants are followed approximately every four years, and thus, have undergone MRI at either their seventh, eighth or ninth examinations, or any combination of the three cycles, ranging between 1999 and 2014.

Out of the 699 SHHS participants, there were 1300 MRI records from 575 participants with ePVS ratings. Records were excluded if they had contraindications for MRI or neurological conditions considered to affect ePVS ratings (such as head trauma, brain tumors, multiple sclerosis, dementia, or stroke). Of note, one included participant had mild cognitive impairment at the time of the sixth clinic examination, while three included participants had mild cognitive impairment at the time of the MRI. After exclusions, 1209 records from 552 participants remained. The earliest available MRI record, and thus, closest to PSG testing, was selected for analysis when multiple were available. Overall, the final sample included 552 participants that had valid PSG and MRI, with time between these two assessments ranging from 1.4 years to 17.7 years. Most participants (89.3%) had an interval up to five years between their PSG and MRI. All participants gave their written informed consent before the beginning of the study. The institutional review board at Boston University Medical Center approved the study.

### 2.2 PSG recording

The procedures and scoring criteria of the in-home all-night PSG were published previously [22–24]. The PSG included electroencephalograms, electrooculograms, electrocardiogram, chin electromyogram, oximetry, chest wall and abdomen inductance plethysomnography, and nasal/oral airflow thermistry. Our primary sleep parameters of interest were sleep stages in absolute minutes, i.e., N1, N2, N3 (or SWS), and REM sleep. We also investigated sleep stages expressed as a percentage of total sleep time, as relative percentages give additional information on the overall structure of sleep. Because other sleep parameters were previously shown to be associated with ePVS burden in smaller clinical populations, we also studied total sleep time, sleep efficiency, wake after sleep onset (WASO), the apnea-hypopnea index (AHI, 4% desaturation criterion for hypopneas scoring), and sleep time spent with oxygen saturation under 90% (SpO2<90%). All sleep parameters were treated continuously.

### 2.3 MRI and ePVS rating

MRI records were measured using a brain-dedicated Siemens Magnetom MRI (1.5T) with parameters and sequences described previously [25]. ePVS are visible on MRI when dilated, and are most often seen in the basal ganglia and centrum semiovale, which contain deep perforating arteries, and thus, were rated in both regions separately in the present study. ePVS were visually graded (by J.R.R. and two other raters) on T2-weighted MRI sequences as per previously described methods [26, 27]. The intra-rater reliability was good to excellent (ICC between 0.74 to 0.81) and inter-rater reliability was excellent (ICC between 0.8 to 0.9) [27]. Briefly, ePVS were identified as being 1) of a signal of similar intensity than cerebrospinal fluid, and 2) that adhered to the course of penetrating vessels. They either appeared as linear or of a round shape and were not larger than 3 mm. All except 12 participants were rated on the coronal view, the rest were rated on the axial view. We recently validated ratings using coronal views, finding that they are highly correlated to ratings using axial views. Four grades were possible depending on the frequency of ePVS: grade 1=0 to 10 counts; grade 2=11 to 20 counts; grade 3= 21 to 40 counts; grade 4=>40 counts. For descriptive purposes, all four grades are presented in Table 1. However, because of the small number of participants with grade 4, ePVS were dichotomized in statistical models as low burden (<20 counts, grades 1 and 2) and high burden (>20 counts, grades 3 and 4).

### 2.4 Stratifying variables

To determine the presence of the *ApoE ε4* allele, the two polymorphic sites of the *ApoE* gene were genotyped from whole blood, amplified by PCR for 35 cycles (DNA Thermal Cycler, PTC-100, MJ Research), and separated by electrophoresis. Participants were classified according to their *ApoE ε4* allele carrier status: at least one *ε4* allele for carriers and no *ε4* allele for non-carriers. Age groups were defined using the cut-off of 60 years old (aged under 60 years vs. those aged 60 years and older). Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or use of antihypertensive medications.

### 2.5 Statistical analyses

Analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC). A two-sided $P<0.05$ was considered statistically significant. Sleep stages (N1, N2, N3 and REM) in absolute minutes and percent of total sleep time were treated as continuous variables. The AHI was log transformed in analysis, as it was left-skewed. Logistic regression models were used to explore the association between sleep architecture and dichotomized ePVS ratings, adjusted for age, sex, time interval between PSG and MRI, hypertension, current smoking, and *ApoE ε4* allele carrier status. All covariates were measured at the clinical examination closer to the PSG. Sleep architecture variables were included in separate models to avoid multi-collinearity issue. First, we sought to evaluate the association between absolute duration of sleep stages with ePVS burden. Secondly, we explore the proportion of sleep stages on total sleep time, total sleep time, sleep efficiency, WASO, the AHI and hypoxia with SpO2<90% in association with ePVS burden.

As exploratory analyses, some of these logistic regression models with sleep stages (absolute duration in minutes), total sleep time, and the AHI were performed again in stratified samples to explore whether these associations varied across subpopulations. Stratified variables were *ApoE ε4* allele carriers vs. non-carriers; those aged under 60 years vs. those aged 60 years and older; as well as in participants with vs. without hypertension. The same covariates were used in this model, although *ApoE ε4* allele carrier status and hypertension status were removed as covariates when they were the stratifying variable. In the stratified analyses, logistic regression models used Firth corrections to account for small sample bias.

## 3. Results

### 3.1 Descriptive characteristics of the sample

The sample demographic, sleep and ePVS characteristics are presented in Table 1. The sample included 552 participants aged between 39 to 81 years old at the time of their clinical exam close to the PSG (43 to 85 at the time of the MRI). The majority of the sample was aged between 45 and 65 years old at the time of the PSG (66.6%). The AHI ranged from 0 to 115 events/hour. In the centrum semiovale, 68 cases of ePVS grades 3 or 4 were observed, while only 21 cases of grades 3 or 4 were observed in the basal ganglia (vs. 48.9% as grade 1 and 38.8% as grade 2). Full grading of ePVS centrum semiovale are presented in Table 1.

### 3.2 Association between ePVS burden and sleep architecture

More N1 sleep (longer absolute duration and higher proportion of total sleep time) was associated with higher ePVS burden in the centrum semiovale (Table 2). Less N3 sleep (shorter absolute duration and lower proportion of total sleep time) were associated with higher ePVS burden in the centrum semiovale, although the latter association was borderline (Table 2). No association between total sleep time, sleep efficiency, N2 sleep, REM sleep, or the AHI was observed with centrum semiovale ePVS burden. No association between sleep parameters and ePVS burden in the basal ganglia was observed.

About 18% of the sample (n=96) used sleeping pills (≥1 time/month) and 5% of the sample (n=30) used antidepressants. Since these medications could affect sleep architecture, we additionally adjusted significant associations (in addition to all previously stated covariates) for the usage of these medications. Results remained unchanged: More N1 sleep (absolute duration, OR [95% CI], 1.03 [1.01–1.05], p=0.011; proportion of total sleep time, 1.11 [1.03–1.20], p=0.004) and less N3 sleep (absolute duration, 0.99 [0.98–1.00], p=0.030; proportion of total sleep time, 0.97 [0.94–1.00], p=0.055) were associated with higher ePVS burden in the centrum semiovale.

### 3.3 Stratification by *ApoE ε4* allele carrier status, age and hypertension

Only ePVS in the centrum semiovale were considered for stratified analyses given the low number of ePVS of grade 3 or 4 for basal ganglia, and stratified associations are presented in Table 3. In *ApoE ε4* allele carriers, 13.8 % (n=16) of participants had a centrum semiovale ePVS grading of 3 or 4, while 12.0 % (n=51) of participants had the same grading in non-carriers. While shorter total sleep time was associated with higher ePVS burden in non-carriers, longer total sleep time was associated with higher ePVS burden in carriers. Moreover, longer absolute REM sleep duration was associated with higher ePVS burden in carriers only, whereas these associations were not observed in non-carriers.

In those aged 60 years and older, 21 % (n=53) of participants had grade 3 or 4 ePVS in the centrum semiovale, while only 5 % (n=15) of participants had the same grade in those aged under 60 years old. Longer N1 duration was associated with higher ePVS burden only in participants that were aged 60 years and older at the time of the PSG, while these associations were not present in younger individuals.

In participants with hypertension, 17.7 % (n=37) had a centrum semiovale ePVS grade of 3 or 4, whereas 8.5 % (n=29) of participants in those without hypertension had same grade. Longer N1 duration was associated with elevated ePVS burden in hypertensive individuals only, whereas this association was not present in non-hypertensive participants.

## 4. Discussion

In the community-based FHS, we observed that lighter sleep, characterized by more N1 sleep and less SWS, was associated with elevated ePVS burden in the centrum semiovale. To our knowledge, this is the largest study to date to explore the association between PSG-derived sleep architecture and ePVS burden. More N1 sleep and less SWS have been associated with cognitive decline and MRI markers of brain aging respectively [28, 29]. These findings suggest that disrupted sleep architecture could be a contributor or a marker of SVD and neurodegeneration partially through poorer glymphatic drainage as evidence by higher ePVS burden.

### 4.1 Previous studies linking sleep characteristics and ePVS burden

Our current findings of less SWS in association with ePVS burden is supported by a few previous studies. In 26 participants evaluated for cerebrovascular diseases, ePVS burden in the basal ganglia was associated with shorter N3 duration [13]. In 36 patients with arteriosclerotic cerebral SVD, decreased frontal delta EEG power, representative of SWS

frequency band, was associated with ePVS in the centrum semiovale [30]. Another group showed that in 63 OSA patients of all severities, a higher ePVS burden correlated with lower SWS and REM sleep proportions [14]. On the other hand, other groups did not show any association between sleep stages measured with PSG and ePVS burden [15, 31]. Although few groups explored sleep stages and ePVS burden, no previous study found an association between more N1 sleep and ePVS burden. As greater N1 sleep could be perceived as wake by sleepers themselves, a study showing that self-reported interrupted sleep was associated with ePVS burden in individuals aged in their 70s [10] could have been due to objectively longer N1 sleep. Moreover, because we observed that more N1 sleep was associated with ePVS burden in older individuals and participants with hypertension specifically, different sample composition could explain inconsistencies between findings, with many previous studies being in varying clinical samples.

We observed that shorter sleep duration was associated with elevated ePVS burden in *ApoE ε4* allele non-carriers whereas more sleep duration was associated with elevated ePVS burden in carriers. In participants with traumatic brain injury, shorter total sleep time measured with PSG was associated with ePVS burden [15]. In patients with history of stroke, self-reported longer sleep duration, greater time in time in bed, and daytime dysfunctions were associated with larger ePVS volume [11]. Both longer and shorter sleep duration have previously been associated with poorer health and cognitive outcomes [32–34], where shorter sleep is generally considered a risk factor for diseases whereas longer sleep duration is seen as a consequence or a compensatory response to health conditions. Thus, it is possible that the presence of pathology (e.g., in *ApoE ε4* allele carriers or in patients with cerebrovascular diseases) increases sleep duration and ePVS burden, whereas shorter sleep duration and lower sleep efficiency may be risks factors for ePVS burden, especially before extensive pathology in non-*ApoE ε4* carriers.

In neither the full sample nor in stratified analysis, we did not observe associations between the AHI nor hypoxia with ePVS burden, which is consistent with a previous study [16]. Other groups showed that hypoxia and arousal [14], the AHI [18], or moderate to severe obstructive sleep apnea [17], were associated with elevated ePVS burden. The proportion of participants presenting with moderate to severe obstructive sleep apnea was low in our sample, and thus, we might have been underpowered to observe an effect.

### 4.2 Potential mechanisms underlying the association between lighter sleep and higher ePVS burden

ePVS are seen as impairments to the glymphatic system of the brain, which is composed by spaces around blood vessels participating in dynamic fluid exchange between the cerebrospinal fluid and the interstitial space [1]. It has been hypothesized that ePVS, as markers of SVD [35], are part of a vicious cycle of neuropathological processes, where accumulation of waste products, inflammation, poorer blood flow, and oxidative stress all lead to loss of pericytes, blood-brain barrier dysfunction, and enlarged ePVS, which leads to progressive impairment in fluid dynamics [1]. Although it may seem counter-intuitive that enlarged rather than reduced PVS are markers of SVD and potential impaired fluid dynamics, ePVS are thought to represent obstruction by waste, protein and cell debris

as well as fluid accumulation due to blood-brain barrier failure and/or failure in draining interstitial space fluid [1]. Indeed, inflammatory cells and amyloid accumulate in the PVS [36, 37]. In patients with SVD, higher ePVS burden is associated with poorer glymphatic function measured diffusion MRI [4]. Hypertension may also contribute to, or be a marker of, impaired perivascular drainage via increase in arterial stiffness and decrease in the pulsatile force promoting perivascular clearance. In a study of rodent animal models, hypertensive animals had lower rates and clearance of perivascular metabolites compared with their normotensive counterpart [38]. However, mechanistic underpinnings of ePVS remains to be explored and confirmed.

Sleep has been hypothesized to be a key factor in fluid dynamics, and could potentially be involved ePVS formation [1]. Our finding of lighter sleep with higher ePVS burden is consistent with the current hypothesis that adequate sleep architecture contributes to glymphatic clearance [8, 9]. Participants with less SWS and more N1 sleep could display poorer glymphatic drainage over time, accumulation of waste products, and subsequent enlargement of PVS. Moreover, as more N1 sleep and less SWS sleep has been associated with higher levels of inflammatory markers [39], this sleep pattern might promote ePVS burden by facilitating an enhanced inflammatory response. Alternatively, ePVS could precede disrupted sleep patterns: higher ePVS burden could contribute to dysfunctions in cerebral regions regulating sleep stages, or a common factor, such as genetics, might determine both sleep patterns and susceptibility to ePVS, as these were shown to be highly heritable [40].

Sleep disturbances are increasingly recognized as risk factors for stroke and dementia [5–7]. Lighter sleep may contribute to poorer glymphatic clearance as evidenced by higher ePVS burden, SVD, and subsequent risk of stroke and dementia. Individuals that were positive for amyloid deposition measured with PET or suffered from a previous stroke had higher ePVS burden in the centrum semiovale [35, 41], although some studies did not confirm this association of ePVS with stroke and cognitive impairment [42]. One group has shown that ePVS burden was associated with 4-year cognitive decline and 8-year risk of dementia in the elderly participants.[2] It has been shown that adequate deep sleep contributes to amyloid clearance from the brain [8], and thus, lighter sleep and subsequent ePVS burden may promote amyloid pathology and Alzheimer’s disease risk. Consistently, higher ePVS burden correlated with cerebrospinal fluid levels of amyloid and tau pathology in patients with chronic insomnia and impaired cognition [19]. Interestingly, we show that associations between lighter sleep were mostly observed in those who already are at higher risk of stroke or dementia (i.e., older individuals, hypertensive participants) suggesting that when lighter sleep is combined with other promoters of SVD and neurodegeneration, it could elevate ePVS burden.

### 4.3 Magnitude of effect and potential implication for the aging brain

Every minute of increase in N1 sleep duration was associated with 3% higher odds or presenting a grade 3 or 4 ePVS, representing 45% higher odds of presenting higher ePVS burden between Q1 and Q3 of N1 sleep duration (interquartile range of 15 minutes). Decrease in SWS of 57 minutes (interquartile range) represents 57% higher odds of

presenting a grade 3 or 4 ePVS rating. In addition to inter-individual variability, sleep architecture is dynamic through development and aging, with N1 sleep increasing and SWS decreasing with age [43], with some individuals retaining deeper sleep than others over time. Therefore, the pattern of disrupted sleep architecture is also reported through aging, and thus, sleep changes as we age may be increasingly more important in the development of ePVS, stroke and dementia. Although higher ePVS burden and changes in sleep stages are observed with aging, all our statistical models were adjusted for age, suggesting that the observed associations may be correlated characteristics of the aging brain, and not incidental findings concomitantly observed in older individuals.

### 4.4 Strengths and limitations

Strengths of the present study include the large community-based sample, the rigorous assessment of sleep architecture using the gold-standard PSG, and blinded assessment of ePVS. Limitations included the single night of PSG, which could have led to a first-night effect in some individuals, although this is probably limited as the PSG was in-home. Moreover, differences in findings from one study to another could be partially due to night-to-night intra-individual variability in sleep characteristics, as well as variability in PSG scoring. Another limitation is the time frame between the PSG and MRI, during which we do not know how obstructive sleep apnea might have evolved and be a source of noise in the analysis with ePVS burden. Although ePVS were rated subsequently to the PSG, we are limited by the lack of pre-PSG ePVS data to infer on causality and direction of association. Indeed, as discussed earlier, lighter sleep could contribute to ePVS formation, and ePVS might contribute to further dysregulated sleep patterns. Moreover, ePVS and glymphatic clearance remain a controversial concept of a complex fluid waste clearance that need to be clarified [1]. Indeed, there are alternative hypotheses that ePVS are a compensatory mechanism to improve clearance. However, ePVS' direct association with pathological states (e.g., stroke risk and presence, hypertension, inflammatory cell accumulation, blood-brain barrier dysfunction) questions this view, although compensatory mechanisms in the face of disease remain possible [1]. We are also limited by the composition of the FHS: participants were primarily of European ancestry, and thus, it is unclear how our findings can be generalizable to other populations. Finally, very few participants had high ePVS burden in the basal ganglia in our large community sample (n=21), and thus, we might have been underpowered to specifically addressed ePVS in that region. Nevertheless, lobar distribution has been attributed to cerebral amyloid angiopathy, while deep distribution to hypertensive arteriopathy [44, 45]. This suggests that different types of SVD might be reflected by ePVS in the centrum semiovale vs. basal ganglia, and thus, it is possible that our observations reflect the relation between sleep with cerebral amyloid angiopathy. However, further longitudinal studies are needed to confirm these findings.

### 4.5 Conclusions

In a large non-clinical community-based sample, we have shown that lighter sleep is associated with higher ePVS burden in the centrum semiovale. Our findings further the hypothesis that sleep architecture is involved in proper fluid dynamics and glymphatic clearance of the brain, which is a potential biological pathway explaining the association between sleep disturbances with stroke and dementia risk. Moreover, we have shown that

there are variations in the population regarding the association of lighter sleep with ePVS burden, suggesting that other stroke and dementia risk factors, such as genetic predisposition and hypertension, may synergically affect glymphatic dysfunction in combination with changes in sleep architecture.

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## Highlights

- More N1 sleep was associated with enlarged perivascular spaces
- This association was especially apparent in hypertension and with aging
- Less slow-wave sleep was also associated with enlarged perivascular spaces
- These findings are consistent with the glymphatic hypothesis of sleep

**Table 1.**

Demographic and PSG characteristics of the full sample and in centrum semiovale ePVS gradings

| Mean (SD) or n(%) | Full sample (n=552) | Centrum Semiovale Grading | | | |
|---|---|---|---|---|---|
| | | Grade 1 n=270 (48.9) | Grade 2 n=214 (38.8) | Grade 3 n=59 (10.7) | Grade 4 n=9 (1.6) |
| ***Demographics*** | | | | | |
| Age at clinic exam (close to PSG), years | 58.6 (8.9) | 55.0 (8.1) | 61.0 (8.3) | 64.9 (7.9) | 68.3 (6.1) |
| Age at MRI, years | 63.0 (8.9) | 59.2 (8.1) | 65.4 (8.1) | 69.9 (7.0) | 74.7 (6.5) |
| Sex, men, n(%) | 278 (50.4) | 145 (54) | 96 (45) | 32 (54) | 5 (56) |
| Time between PSG and MRI, years | 3.4 (2.3) | 3.2 (1.9) | 3.4 (2.2) | 4.2 (3.8) | 5.2 (3.0) |
| *ApoE e4* allele carrier status, n(%) | 116 (21.5) | 53 (20) | 47 (23) | 15 (26) | 1 (11) |
| Current smoking, n(%) | 75 (13.6) | 37 (14) | 29 (14) | 7 (12) | 2 (22) |
| Hypertension, n(%) | 209 (38.0) | 80 (30) | 92 (43) | 32 (56) | 5 (56) |
| ***PSG*** | | | | | |
| Total sleep time, min | 375.3 (57.3) | 381.6 (52.3) | 372.7 (56.8) | 360.0 (68.2) | 319.0 (105.9) |
| Sleep efficiency, % | 83.4 (9.6) | 84.6 (9.0) | 83.0 (8.8) | 79.7 (12.5) | 78.0 (16.8) |
| WASO, min | 54.9 (40.7) | 49.5 (34.0) | 59.0 (42.4) | 66.5 (49.5) | 42.3 (83.0) |
| N1 sleep, min | 18.9 (12.8) | 18.3 (12.3) | 18.2 (12.2) | 22.6 (14.5) | 28.7 (21.8) |
| N1 sleep, % | 5.0 (3.4) | 4.8 (3.1) | 4.9 (3.3) | 6.2 (4.0) | 8.8 (6.6) |
| N2 sleep, min | 210.7 (50.7) | 214.0 (47.4) | 206.8 (53.7) | 210.4 (51.1) | 204.6 (70.1) |
| N2 sleep, % | 55.7 (11.2) | 55.7 (10.5) | 55.2 (12.0) | 57.4 (11.7) | 59.2 (7.3) |
| N3 sleep, min | 70.3 (42.2) | 70.2 (38.3) | 74.8 (45.8) | 57.6 (43.2) | 53.7 (42.7) |
| N3 sleep, % | 18.6 (10.9) | 18.2 (9.7) | 19.9 (11.7) | 16.1 (12.4) | 15.8 (12.4) |
| REM sleep, min | 79.2 (27.1) | 82.9 (27.1) | 76.1 (24.8) | 76.8 (31.1) | 54.2 (31.1) |
| REM sleep, % | 20.7 (5.9) | 21.4 (5.9) | 20.1 (5.6) | 20.4 (6.7) | 16.2 (8.5) |
| Time spent with $SpO_2$<90%, % | 2.7 (8.2) | 1.9 (4.6) | 2.6 (1.5) | 5.8 (16.8) | 9.6 (14.4) |
| Obstructive Apnea-Hypopnea index (4%), events/hour | 8.9 (12.7) | 8.4 (13.2) | 8.9 (12.2) | 11.3 (12.5) | 10.1 (11.1) |
| None (AHI <5), % | 271 (52.8) | 148 (58) | 9 8 ( 4 9) | 2 1 (40) | 4 (5 0) |
| Mild OSA (AHI 5–15), % | 146 (28.5) | 62 (24.4) | 66 (33.3) | 17 (32.1) | 1 (12.5) |
| Moderate OSA (AHI 15–30), % | 67 (13.1) | 30 (11.8) | 22 (11.1) | 12 (22.6) | 3 (3.8) |
| Severe OSA (AHI 30+), % | 29 (5.7) | 14 (5.5) | 12 (6.1) | 3 (5.7) | 0 (0) |

AHI, apnea-hypopnea index; *ApoE e4*, apolipoprotein E4 allele; ePVS, enlarged perivascular spaces; PSG, polysomnography; MRI, magnetic resonance imaging; OSA, obstructive sleep apnea; REM, rapid-eye movement.

**Table 2.**

Association between sleep characteristics and ePVS ratings

| Sleep characteristics | ePVS ratings | | | |
|---|---|---|---|---|
| | Basal ganglia | | Centrum semiovale | |
| | *OR (95% CI)* | *P* | *OR (95% CI)* | *P* |
| Total sleep time, min | 1.00 (0.99–1.01) | 0.663 | 1.00 (0.99–1.00) | 0.333 |
| Sleep efficiency, % | 0.99 (0.93–1.05) | 0.763 | 0.99 (0.95–1.02) | 0.433 |
| WASO, min | 1.00 (0.99–1.01) | 0.775 | 1.00 (1.00–1.01) | 0.631 |
| Apnea-Hypopnea index, events/hour | 0.87 (0.54–1.39) | 0.552 | 1.12 (0.84–1.50) | 0.434 |
| Time spent with $SpO_2$<90%, % | 1.00 (0.96–1.05) | 0.929 | 1.02 (0.99–1.05) | 0.153 |
| N1 sleep, min | 1.01 (0.97–1.05) | 0.628 | 1.03 (1.01–1.05) | **0.008** |
| N1 sleep, % | 1.03 (0.90–1.18) | 0.710 | 1.12 (1.04–1.20) | **0.003** |
| N2 sleep, min | 1.00 (0.99–1.01) | 0.988 | 1.00 (1.00–1.01) | 0.839 |
| N2 sleep, % | 1.00 (0.96–1.05) | 0.985 | 1.01 (0.98–1.04) | 0.487 |
| N3 sleep, min | 1.00 (0.99–1.01) | 0.971 | 0.99 (0.98–1.00) | **0.028** |
| N3 sleep, % | 0.99 (0.95–1.04) | 0.734 | 0.97 (0.94–1.00) | 0.055 |
| REM sleep, min | 1.00 (0.99–1.02) | 0.724 | 1.00 (0.99–1.01) | 0.807 |
| REM sleep, % | 1.01 (0.94–1.10) | 0.746 | 1.01 (0.96–1.05) | 0.791 |

Basal ganglia and centrum semiovale ePVS rating are scored from Grade 1 to 4 (mild to severe) as a 2-level variable: grade 1 and 2 versus 3 and 4. Models were adjusted for age, sex, time interval between PSG, *ApoE ε4* carrier status, hypertension, and smoking. ePVS, enlarged perivascular spaces; REM, rapid-eye movement. The apnea-hypopnea index was log-transformed.

**Table 3.**

Stratified associations between sleep parameters and centrum semiovale ePVS burden

| Sleep characteristics | OR; 95%(CI); p | | | | | |
|---|---|---|---|---|---|---|
| | *ApoE ε4* carrier status | | Age | | Hypertension status | |
| | *Non-carriers* | *Carriers* | *<60 years old* | *≥60 years old* | *Non-hypertensive* | *Hypertensive* |
| ***Total sleep time, min*** | 0.99 (0.99–1.00) **p=0.043** | 1.02 (1.00–1.03) **p=0.037** | 1.00 (0.98–1.01) p=0.755 | 1.00 (0.99–1.00) p=0.297 | 0.99 (0.98–1.00) p=0.069 | 1.00 (0.99–1.01) 0.545 |
| ***Apnea-Hypopnea index, events/hour*** | 1.22 (0.87–1.72) p=0.253 | 0.91 (0.53–1.55) p=0.726 | 0.96 (0.54–1.68) p=0.878 | 1.20 (0.86–1.69) p=0.285 | 1.42 (0.90–2.24) p=0.136 | 0.98 (0.68–1.41) p=0.895 |
| ***N1 sleep, min*** | 1.02 (1.00–1.05) p=0.055 | 1.04 (1.00–1.07) p=0.059 | 1.02 (0.98–1.06) p=0.299 | 1.03 (1.01–1.05) **p=0.017** | 1.01 (0.98–1.04) p=0.426 | 1.04 (1.01–1.07) **p=0.009** |
| ***N2 sleep, min*** | 1.00 (0.99–1.00) p=0.561 | 1.01 (1.00–1.02) p=0.074 | 1.00 (0.99–1.01) p=0.964 | 1.00 (0.99–1.01) p=0.952 | 1.00 (0.99–1.01) p=0.542 | 1.00 (1.00–1.01) p=0.498 |
| ***N3 sleep, min*** | 0.99 (0.98–1.00) p=0.107 | 0.99 (0.98–1.00) p=0.182 | 1.00 (0.98–1.01) p=0.645 | 0.99 (0.98–1.00) p=0.050 | 0.99 (0.98–1.00) p=0.127 | 0.99 (0.98–1.00) p=0.241 |
| ***REM sleep, min*** | 0.99 (0.98–1.00) p=0.172 | 1.02 (1.00–1.05) **p=0.016** | 1.01 (0.99–1.03) p=0.158 | 1.00 (0.98–1.01) p=0.657 | 0.99 (0.98–1.01) p=0.285 | 1.01 (0.99–1.02) p=0.240 |

Centrum semiovale ePVS rating are scored from grades 1 to 4 (mild to severe) as a 2-level variable: grades 1 and 2 versus 3 and 4. Models were adjusted for age, sex, time interval between PSG, *ApoE ε4* carrier status, hypertension, and smoking. *ApoE ε4* allele carrier status and hypertension status were removed as covariates when they were the stratifying variable. ePVS, enlarged perivascular spaces; REM, rapid-eye movement.