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Effects of Sleep on Brain Perivascular Space in a Cognitively Healthy Population

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Abstract

The magnetic resonance imaging (MRI) visible perivascular space (PVS) reportedly clears amyloid-β and metabolic waste during sleep. Previous studies reported an association between sleep and the PVS in small vessel disease, traumatic brain injury, and Alzheimer's disease. However, this relationship in a healthy cohort is still unclear. Here, we used the Human Connectome Project Aging dataset to analyze the relationship between sleep and the PVS in cognitively healthy adults across the aging continuum. We measured sleep parameters using the self-reported Pittsburgh Sleep Quality Index questionnaire. We found that older adults who had better sleep quality and sleep efficiency presented with a larger PVS volume fraction in the basal

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N.S., G.B., K.L., W.M., F.S., and J.C. conceived the research study. N.S., and J.C. analyzed and interpreted the data. N.S. wrote the manuscript. G.B., K.L, W.M., F.S. and J.C. reviewed the manuscript critically. All authors edited and revised the manuscript and approved final submission.

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Credit author statement

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ganglia (BG). However, sleep measures were not associated with PVS volume fraction in the centrum semiovale (CSO). In addition, we found that body mass index (BMI) influenced the BG-PVS across middle-aged and older participants. In the entire cognitively healthy cohort, the effect of sleep quality on PVS volume fraction was mediated by BMI. However, BMI did not influence this effect in the older cohort. Furthermore, there are significant differences in PVS volume fraction across racial/ethnic cohorts. In summary, the effect of sleep on the PVS volume alteration was different in the middle-aged adults and older adults.

Keywords

body mass index; magnetic resonance imaging; perivascular space; race; sleep

1. Introduction

The perivascular space (PVS), also called the Virchow-Robin space, is a fluid-filled space around blood vessels in the brain[1]. The PVS is thought to clear cerebral metabolic waste through the aquaporin-4 (AQP4) channel expressed on the endfeet of astrocytes[2–4]. AQP4, an astrocytic water channel in the glymphatic system, is one of the key factors regulating parenchymal cerebrospinal fluid (CSF) influx and interstitial amyloid-β (Aβ) deposition. The deletion of AQP4 or low AQP4 expression reportedly led to chronic sleep disruption in mice, resulting in severe neurodegeneration in the hippocampus and decreased working memory[5,6].

Magnetic resonance imaging (MRI)-visible PVSs are associated with aging, body mass index (BMI), hypertension, and neuroimaging findings of small vessel disease[1,7]. The majority of previous MRI investigations suggest that higher PVS number and larger PVS volume in the brain white matter is either a sign of pathology, or the normal physiological process in healthy aging. Previous research has shown that PVS visibility increases with age[8]. Enlarged PVS volumes have also been reported to have a positive association with sleep disturbance in populations with small vessel disease, traumatic brain injury, and Alzheimer's disease[9,10].

As PVS is better visible in the basal ganglia (BG) and centrum semiovale (CSO) when PVS is enlarged[11], most MRI studies on the PVS focus on the PVSs in these two regions. Moreover, findings from previous studies indicated that morphology of PVSs in specific anatomical areas of the brain have been positively associated with several neurological disorders, such as small vessel disease and Alzheimer's disease (AD) and cognitive decline[1,12,13]. Some studies have demonstrated that higher MRI-visible BG-PVSs count are associated with arteriosclerosis, vascular cognitive impairment, and cognitive decline in Parkinson's disease[14–16]. In addition, enlarged CSO-PVS volumes are associated with AD and cerebral amyloid angiopathy[15,17–20]. These findings highlight the clinical significance of the anatomical distribution and morphology of the PVS, and their importance in neurological health.

As researchers delve deeper into understanding the mechanisms that underlie brain health, recent animal model studies show that the glymphatic system plays a major role in clearing

metabolic waste during sleep[21,22]. In animal models, it has been shown that enlargement of the PVS is linked to impaired waste clearance[23] This, in turn, obstructs the removal of harmful metabolic byproducts such as Aβ, leading to neurological damage to the brain[24]. In human studies, one night of sleep deprivation or deep sleep interruption resulted in an increase in Aβ deposition observed under positron emission tomography imaging and an increase in Aβ in the CSF of the lumbar spine, respectively[25,26] There is also evidence from both human and animal studies that sleep position is associated with brain clearance alternation. For example, head position during sleep was also found to impact the glymphatic clearance function in humans[27,28]. In addition, supine sleep position occurred more frequently in patients with neurodegenerative diseases compared to healthy controls[27]. In one animal study, the glymphatic clearance was shown to be more efficient in the lateral sleep position[28]. These observations have prompted researchers to investigate the relationship between the PVS and sleep in humans. The development of neurodegenerative diseases has been linked to sleep deprivation. Specifically, studies have reported associations between 'Rapid eye movement and Behavioral sleep Disorder' (RBD) to disorders such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and AD[29,30]. A small body of research documents a positive relationship between PVS volume and sleep interruptions[31,32]. Del Brutto and colleagues found enlarged BG-PVSs in populations who had poor sleep efficiency[33]. Polysomnography (PSG)-based studies demonstrated an association between a greater number of PVSs and a lower total sleep time[32,34,35]. It has also been found that patients with severe sleep apnea have larger PVSs[34]. On the other hand, one study found that longer time in bed was associated with larger total PVS volume in patients with cerebrovascular disease, supporting a hypothesis of compensatory regulation between the time in bed, sleep time, and sleep quality[36].

These observations reflect an association between poor sleep and the structure and possibly the function of PVSs in different diseases. However, the association between sleep and PVS and the impact of this relationship on the cognitive status of a healthy adults remain unclear. Therefore, in this study we used MRI data from the Human Connectome Project Aging (HCP-Aging)[37] dataset to investigate the relationship between sleep, PVS volume, and cognitive status in a healthy cohort of adults. Sleep parameters used in this study were assessed using the subjective self-reported Pittsburgh Sleep Quality Index (PSQI) questionnaire[38]. Most prior research has focused on diseased populations; while this study investigates the association of sleep with PVS morphology in a cognitive healthy population. Identifying and understanding the association of sleep behavior with the brain-wide distribution of brain clearance alterations in cognitively normal subjects will stimulate new avenues of research and therapeutic development and identify possible new measures to assess interventional efficacy.

Our study aimed to describe the relationship between sleep and PVS in BG and CSO regions in a cognitively normal aging population. Using the Enhanced PVS Contrast (EPC) imaging approach[39], we identified and quantified PVS morphological features. Analysis of sleep quality, sleep efficiency, and PVS changes in BG and CSO was conducted using multivariable regression models. Furthermore, we examined whether the effect of sleep on PVS affected cognitive performance. We also examined the morphology of PVS in relation

to body mass index (BMI), race, and ethnicity. For further research on PVS and sleep, this study will provide a normative reference.

2. Material and Methods

2.1 Participants

We used MRI data from 725 cognitively healthy participants (36–100 years old) from the HCP-Aging Lifespan Release 2.0[37]. At the time of recruitment, participants in the sample were in good health, with no diagnosed history of neurologic or major psychiatric disorder. The HCP-Aging dataset focuses on recruiting participants who exhibit normal health status relevant to their respective age groups and excluded individuals with neurological diseases, including diagnosed AD and symptomatic stroke, that could complicate data analysis. Exclusion criteria for the HCP-Aging dataset did not include sleep behavior, so participants with the PSQI score greater than 5 (which indicates sleep disorder) were still considered cognitively healthy. For cognitive testing, participants with Montreal Cognitive Assessment (MoCA) scores below 19 were excluded from the HCP-Aging dataset. Participants who scored between 20 and 30 were still considered healthy aging, even though a MoCA score below 25 is considered to reflect mild cognitive impairment (MCI)[40] in conventional scoring.

In our analysis, we included age, sex, race, body mass index (BMI), sleep measured by the PSQI[38], and cognitive status measured by the MoCA[40] (more details are provided in Supplement Method), and NIH toolbox working memory tests. The exclusion criteria for the current analysis were: (a) missed T1-weighted MPRAGE (T1W) and T2-weighted SPACE (T2W) MR images (n=170), (b) inferior MRI and PVS quality (n=25), and (c) missed PSQI data (n=17). Consequently, a total number of 513 participants were included in the analysis. We categorized the participants by age as middle-aged adults (36–65 years old, N=363), or older adults (above 65 years old, N=150). The demographic information of the participants is shown in Table 1.

2.2 MRI Acquisition

All participants were scanned using a customized Siemens 3T Prisma scanner housed at Washington University in St. Louis, using a standard 32-channel Siemens receive head coil. The T1W image was acquired with repetition time (TR)/inversion time (TI) = 2500/1000 ms, time to echo (TE) = 1.8/3.6/5.4/7.2 ms, field of view (FOV) = 256 × 240 × 166 mm and the T2W image with TR= 3200 ms, TE= 564 ms, FOV= 256 × 240 × 166 mm.

2.3 MRI pre-processing

Structural T1w MPRAGE and T2w SPACE images were preprocessed in parallel with a LONI pipeline[41] using the HCP minimal processing pipeline version 4.0.1[42] and Freesurfer version 6. The preprocessing steps started by gradient nonlinearity corrections. Structural images were registered together, then brought into native space anterior commissure-posterior commissure alignment, and then registered to MNI space using FSL's FNIRT[43]. The native space images were used to generate individual regional subcortical PVS features

for white and pial surfaces using FreeSurfer[44]. Extensive description of the minimal preprocessing applied can be found in a prior publication[42].

2.4 PVS segmentation and quality control

PVS segmentation was performed as explained in Sepehrband et al.[39] In brief, T1w and T2w images were adaptatively filtered to remove the high-frequency noise and then co-registered and combined to obtain enhanced PVS contrast (EPC). EPC is shown to provide superior visibility of PVS compared with T1w or T2w alone[39]. PVSs were segmented from EPC images (Figure 1a) by applying Frangi filter[45] using Quantitative Imaging Toolkit[46] and a vesselness threshold, which was optimized for the HCP data.[37] To verify the accuracy of PVS segmentation, PVS segmentation quality control was performed by four trained analysts. Evaluation criteria included motion, image quality, and white matter hyperintensity (WMH) severity. The rating scale was from 1 to 3. 1 indicates good quality without motion and ringing, and 3 shows poor image contrast or severe motion and ringing. Images with a score of 3 were excluded from this study.

2.5 Regions of interest (ROIs)

We used the BG and CSO as our regions of interest (ROIs), which are the most common regions where enlarged PVS are visible on MRI, as segmented by FreeSurfer. Based on the guideline of FreeSurfer 'Desikan-Killiany' cortical atlas[47], areas "5001-Left-UnsegmentedWhiteMatter" and "5002-Right-UnsegmentedWhiteMatter" are the regions corresponding to the CSO. Although these two regions contain most of the CSO, they do not include most of the white matter areas underlying the cortex (Figure 1b). On MRI, the CSO-PVSs become visible immediately inferior to the cortical layer, where they run centripetally from the external part of the white matter towards the lateral ventricles[1]; we therefore added to the FreeSurfer CSO mask the white matter areas underlying the following cortical regions: the caudal middle frontal, inferior parietal, pars opercularis, pars orbitalis, pars triangularis, postcentral, precentral, rostral middle frontal, superior frontal, superior parietal, and supramarginal regions in both the right and left hemispheres (Figure 1b). We have previously demonstrated that these regions also contain a significant amount of MRI-visible PVSs in healthy young adults[7]. BG were segmented using an atlas-based approach[48,49]. Brain volume and white matter masks were derived from the Desikan-Killiany atlas[47].

2.6 Sleep parameters

All sleep parameters were assessed using the PSQI[38], which is a 19-item self-rated questionnaire for evaluating subjective sleep quality based on the participant's sleep pattern during the previous month. PSQI items are scored from 0 to 3, with higher scores representing poor sleep behavior. We computed the sleep efficiency score based on component 4 of the PSQI, which evaluates the participant's habitual sleep efficiency. Sleep efficiency is calculated as the proportion of total sleep time divided by the duration spent in bed. The 4-level sleep efficiency score was derived from this as: 0 (proportion> 85%), 1 (proportion 75–84%), 2 (proportion 65–74%), and 3 (proportion<65%). The sleep quality score is computed by component 1 of the PSQI, which evaluates the subjective sleep quality, scored as 0 (sleep quality very good), 1 (sleep quality fairly good), 2 (sleep quality fairly poor), and 3 (very poor sleep quality). The duration of sleep is derived by question 4 of

the PSQI, scored as 0 (sleep time>7 hours), 1 (6–7 hours), 2 (5–6 hours), and 3 (<5 hours). The sleep latency score is computed by component 2 of the PSQI, which evaluates the time required to initiate sleep, alongside its frequency. The 4-level derived score is 0 (less than 15 minutes to fall asleep, or no problem falling asleep during the past month), 1 (16–30 minutes to fall asleep, or if have problem falling asleep less than once per week), 2 (31–60 minutes to fall asleep, or if have problem falling asleep occurs once or twice a week), and 3 (>60 minutes to initiate sleep or experiences delayed sleep 3 or more times per week). Sleep medication is computed by component 6 of the PSQI, which evaluates use of sleep medication, scored as 0 (did not use sleep medication in the past month), 1 (used sleep medication less than once a week), 2 (sleep medication taken once or twice weekly), and 3 (used sleep medication 3 or more times per week). The time in bed is computed by question 1 and 3 of the PSQI. Daytime dysfunction is computed by component 7 of the PSQI, which evaluates the ability to stay awake and maintain enthusiasm, scored as 0 (no problem to keep awake and enthusiasm), 1 (have very slight problem), 2 (somewhat of a problem), and 3 (have a very big problem). The PSQI total score is computed by adding each sleep components. The score ranges from 0 to 21; a higher overall scores indicates worse sleep quality.

2.7 Statistics

We used the fraction of the ROI volume that is occupied by the PVS as our measure to calculate the PVS burden in the BG and the CSO. Owing to the non-normal distribution of the PVS in the BG, the log-transformed value of the volume fraction of the PVS was used.

We used SPSS software version 26.0 (IBM SPSS Inc., Armonk, NY, USA) to perform the correlation, multivariable linear regression, and used R software to conduct the mediation analysis. First, the Mann-Whitney U, and t-tests were used to compare PVS volume fraction and sleep measurements between individuals of different ages. The ANOVA test was applied to compare PVS volume fraction by race (African American, Asian, White, and more than one race) and ethnicity (participants who self-identified as Hispanic /Latino or not). All multiple comparison p-values were corrected via Tukey's HSD multiple comparisons adjustment. Two-sided p-values < 0.05 were considered statistically significant (Table 1).

Next, we used multivariable linear regression analysis to investigate the association between PVS volume fraction (dependent variable) and sleep measurements (independent variables), including sleep efficiency score, sleep quality score, and sleep duration. Age, sex, race/ethnicity, and BMI were used as covariates in the regression models. Aging plays an important role in the PVS volume[50], and aging is also associated with a decreased ability to maintain sleep[51]. On the other hand, the amount of sleep required by people of different age groups also varies[52]. In our initial analysis, we used age as a continuous variable to investigate the relationship between sleep measurements (from PSQI) and PVS in a regression. We found a significant interaction between sleep measurements and age (data not shown). Therefore, we hypothesized that the magnitude of association between sleep and PVS might differ according to age. To better illustrate the differential sleep-PVS associations by age in the subsequent analysis, we categorized the participants by age into the following two groups: middle-aged adults (36–65 years old, N=363), and older adults

(above 65 years old, N=150). We followed the cutoff age range used in papers[53–55] in our analysis. We used dummy variables to analyze the influence of other explanatory variables, including age group, sex, and race/ethnicity categories on the PVS volume fraction; we used age group as a binary variable (middle-aged represented with 1 vs. older aged represented with 0). To test if the association between sleep and PVS differed in middle-aged adults versus older adults, we added interaction terms between age group and sleep measurements into the regression model.

Furthermore, we used the R causal mediation analysis package to investigate the mediation pathways between sleep, PVS volume fraction, MoCA score (cognitive status) and BMI. We used model 4 in the mediation model of Preacher and Hayes[56] to evaluate whether the sleep measured by the PSQI and cognitive performance measured by the MoCA test were mediated by the PVS variable. We calculated the percent mediation, which assesses the change in the direct sleep-cognitive performance effect with the inclusion of a mediator, PVS volume fraction (Figure 2a). In addition, we noted that BMI was also significantly associated with PVS volume fraction in the regression model. A previous study found that poor sleep was associated with a higher BMI over time, and high BMI was associated with shorter sleep duration[57]. Therefore, we also explored the mediation pathways between sleep, PVS volume fraction, and BMI. We calculated the percent mediation, which assesses the change in the direct Sleep-PVS effect with the inclusion of a mediator, BMI (Figure 2b).

3. Results

The demographic characteristics of the study cohort are shown in Table 1. There are more female participants than male (p=0.031). We found that older participants had significantly larger intracranial volume (p<0.0001), BG-PVS volume (p<0.0001) and CSO-PVS volume (p<0.0001) than middle-aged participants. In contrast, middle-aged participants had significantly larger BG volume (p<0.0001) and CSO volume (p<0.0001) than older participants. For sleep measurements, middle-aged participants had higher sleep quality score (p=0.046), longer sleep duration (p=0.017), and lower score for sleep medication (p<0.003). PSQI total score, sleep efficiency score, sleep latency score, time in bed, and daytime dysfunction were not significantly different between middle-aged and older participants. With respect to cognitive performance, older participants had significantly lower MoCA score (p=0.012) and higher working memory score (p=0.005) than middle-aged participants.

3.1 Association between sleep and PVS in different age groups

We investigated the relationship between sleep measures and the PVS volume fraction among each age group using multivariable linear regression. We found that the sleep quality score was significantly negatively associated with the BG-PVS volume fraction among the older (beta= −0.048, p=0.001), and in middle-aged adults (beta=−0.001, p=0.86) (Figure 3a), indicating that poorer sleep quality (higher sleep quality score) is associated with smaller PVS volume fraction. The statistically significant interaction by age group (p=0.005) showed that the sleep quality-BG-PVS association is stronger for older persons than for middle-aged persons (Figure 3b).

We also found that the sleep efficiency score was significantly negatively associated with the BG-PVS volume fraction in the older age group (beta=−0.023, p=0.037), indicating that poorer sleep efficiency (higher sleep efficiency score) was associated with lower PVS volume. In contrast, sleep efficiency score was positively associated with BG-PVS in the middle-aged group (beta=0.002, p=0.64) (Figure 3c). However, the interaction coefficient was not statistically significant (interaction beta = 0.025, p=0.060) (Figure 3d).

Our analysis showed no significant association between the BG-PVS volume fraction and sleep duration, sleep latency score, sleep medication, daytime dysfunction, or total PSQI score (Supplement Table 1). There were also no significant associations between the CSO-PVS volume fraction and sleep measurements (Supplement Table 1).

3.2 The association between sleep quality, sleep efficiency, and BG-PVS in the older age group

Analyzed in the older age group alone (above 65 years old), the BG-PVS volume fraction had a significant negative association with the sleep quality score (beta=−0.046, p= 0.027) and sleep efficiency score (beta=−0.023, p=0.037) (Figure 3). According to the PSQI, a higher sleep measure score corresponds to poorer sleep behavior. Therefore, these results indicate that older participants who had better sleep quality and sleep efficiency has higher BG-PVS volume fraction.

Our next step was to conduct a mediation analysis to uncover the relationship between sleep quality, BG-PVS, and cognitive status. Results of the mediation analysis indicated that there was no mediating effect of the BG-PVS volume fraction in the association between the sleep quality and MoCA scores (Figure 4a, average causal mediation effect (95% CI)= −0.0024 (−0.03,0.03), p=0.94). In addition, no mediating effect of the BG-PVS volume fraction on the association between the sleep efficiency and MoCA scores was observed (Figure 4b, average causal mediation effect (95% CI)= −0.0010 (−0.03,0.02), p=0.83).

3.3 The relationship between sleep quality, BG-PVS, and BMI

In the regression model, we found a statistically significant positive association between BMI and BG-PVS volume fraction (Figure 3a, 3c) and between BMI and CSO-PVS volume fraction (data not shown). Therefore, we hypothesized that BMI might have a mediating effect on the relationship between sleep quality and PVS volume fraction. In the mediation analysis including all participants of the study (N=513), and adding age as a covariate, the sleep quality score was significantly and positively associated with BMI (p=0.0005). In addition, BMI was significantly and positively associated with BG-PVS volume fraction (p<0.0001). The mediation analysis showed a significant indirect effect of the sleep quality score on the BG-PVS volume fraction through BMI (Figure 5a; average causal mediation effect (95% CI)= 0.0027 (0.0005,0.01), p=0.012). However, the direct association between sleep quality score and BG-PVS was not significant (p=0.17). When we limited the analysis to the middle-aged cohort (N=361), there was no mediation effect of sleep quality on BG-PVS, mediated through BMI (Figure 5b, mediation effect (95% CI)= 0.0024 (−0.0008,0.01), p=0.14), but BMI was significantly positively associated with BG-PVS volume fraction (p=0.0005). In contrast, among the older participants (N=150), the sleep quality score had a

significant positive association with BG-PVS volume fraction (p=0.016). Similarly, the BMI had a significant positive effect on BG-PVS volume fraction (p=0.011). However, there was no significant mediation effect through BMI in the older cohort on the association between sleep quality score and BG-PVS volume fraction (Figure 5c, average causal mediation effect (95% CI) = 0.0062 (−0.0007, 0.01), p=0.07). There was not any mediation effect of BMI observed in the association between sleep efficiency and BG-PVS volume fraction. (Supplement Figure 1).

3.4 PVS across race and ethnicity

PVS volume fractions were also observed to significantly differ among racial and ethnic groups (Figure 3a, 3c). As the incidence of cerebrovascular diseases is significantly higher in African Americans compared to Caucasians[58], we further investigated the effect of race/ethnicity on the association between the PVS volume fraction and sleep measurements. We did not find significant interactions between sleep parameters and races/ethnicity (p>0.21). In more detail, the results of ANOVA showed that Asians (p=0.006), African Americans (p<0.0001), and other races (p=0.040) all had significantly smaller BG-PVS volume fraction than Whites. (Figure 6a). CSO-PVS volume fractions did not differ across racial/ethnic groups (data not shown).

4. Discussion

Many studies have shown the different mechanisms of glymphatic clearance during sleep[27,33,36]. In the current study, variation in PVS volume alterations were observed across age and racial/ethnic groups. However, the actual mechanisms causing the different patterns of PVS morphology across age, race, and ethnicity that we observed are still unknown. We plan to study these mechanisms in the future using larger scale datasets and investigate the relationship between PVS and sleep in subregions of white matter CSO.

In this study, we analyzed the relationship between sleep and PVS volume fraction in the BG and CSO in a healthy aging cohort. Overall, we found that different sleep behaviors were associated with the PVS volume fraction in the BG in the older age group but not in the middle-aged group. In addition, we did not find an association between sleep and PVS in the CSO. After categorizing our population into middle-aged (36–65 years old) and older groups (above 65 years old), we found that there were different patterns of association between sleep measures and PVS volume fraction in the BG by age. We found that better sleep quality and sleep efficiency, as indicated by lower scores in the corresponding PSQI components, were associated with larger BG-PVS volume fraction. Our results in the healthy older group were in contrast to the results in the previous PVS studies with diseased samples, where poor sleep was found to be associated with enlarged BG-PVS[32,36]. Our hypothesis is that there are pathological and physiological PVS such that the pattern of change in PVS may differ. In healthy persons, larger PVS may be a sign of better brain clearance.

One possible explanation for the contradictory results could be related to the different mechanisms of PVS for healthy adults on removing metabolic waste from the brain. A recent review article suggested that sleep and glymphatic function may interact differently

in healthy adults than in animal models[59]. As sleep has been shown to drive metabolite clearance from the adult brain[60], it is possible that a large amount of fluid in BG-PVS might indicate a higher rate of fluid exchange and an efficient waste clearance, as previously proposed[61]. On the other hand, in patients with cerebrovascular diseases[32,36], the negative correlation between BG-PVS volume and sleep efficiency might indicate either a compensatory mechanism where accumulation of fluid is a consequence of the perivascular/glymphatic system dysfunction determined by lower sleep efficiency. Lysen et al. found that higher sleep efficiency was associated with higher CSO-PVS counts in a middle- to old-aged participants[61]. However, the association of the sleep efficiency and the CSO-PVS volume fraction in the middle-aged healthy population was not significant in our study. Another possible reason for the contrary results we found could be due to our mapping all PVSs rather than only PVSs larger than a certain diameter. Using the high-resolution images of the HCP-Aging dataset and the accuracy of PVS segmentation by EPC technique, we detected higher PVS volume fraction compared to other studies[39]. Moreover, it is also possible that the findings might be impacted by variations across studies in sleep assessment methods and PVS measurement methods[59].

We did not find a significant association between sleep and CSO-PVS. One explanation could be that CSO is a large brain region, and some subregions may have an association with sleep, while others do not, thus cancelling one another out on the final outcome. Therefore, future research is needed on the association between sleep and PVS in subregions of the CSO.

In our mediation analysis, we noted that BMI plays a role in mediating the relationship between sleep and BG-PVS volume in the entire healthy cohort (N=513). This cohort shows that BMI has a larger association to BG-PVS than sleep. This is consistent with a previous study showing a significant positive correlation between BMI and PVS volume fraction in a young participants (22–37 years old)[7]. Recent research found a positive association between visceral fat, MRI-visible PVS and white matter lesions in the brain[62]. Currently, it is unknown exactly how BMI is linked to PVS, but it may be related to higher intracranial pressure, since CSF pressure correlates linearly with BMI[11]. Alternatively, the BMI-PVS association may be linked to reduced vascular contractility and vascular dysfunction that is often associated with obesity[11]. It is worth noting that the relationship between the BG-PVS volume fraction and sleep was not mediated by BMI status in the older population (N=150), although the sample size was smaller than the whole sample, there was the trend towards marginal significant (p=0.07). One potential explanation is that body fat mass increases while lean body mass and bone mineral density decrease in the older adults, so that body fat may be underestimated by BMI in the older study participants[63]. In another mediation model between sleep, BMI, and BG-PVS, we tested sleep quality as the mediator and BMI as the predictor of BG-PVS. However, no mediation was found (data not shown). These findings suggest that BMI may influence the association of the PVS and sleep in various ways.

We also investigated the association of the sleep measurements on the PVS by race and ethnicity. Sleep quality did not significantly interact with race/ethnicity; however, the BG-PVS volume fraction did significantly differ by race. One previous study reported larger dilated BG-PVS volume in Whites, compared to African Americans, Asians, and other racial

participants[64]. In line with this result, we found that Whites had significantly larger BG-PVS volume fraction than Asians, African Americans, and other racial groups (Figure 6a). In addition, Hispanics or Latinos had smaller BG-PVS than other ethnic groups (Figure 6b). There was no difference for CSO-PVS volume fraction by race. This is the first study to demonstrate the association of the PVS volume fraction and sleep in a racially/ethnically diverse sample. These findings should be investigated cautiously with additional social and biological factors, as the mechanism and association between race and PVS is still not fully investigated. These data from the HCP-Aging dataset provide initial insight of the potential differences, and more studies are necessary.

In this study, we investigated how PVS alterations and sleep were associated with cognitive status. In the mediation analysis for older age group, we observed the trend of higher BG-PVS volume fraction and better cognitive status in older participants who had poor sleep quality; however, there was no significant causal mediation effect between the BG-PVS volume fraction and cognitive status. Moreover, there was no significant association between the PVS and the results of the NIH toolbox working memory test (data not shown). Other findings in the literature also showed that the higher PVS burden is not associated with cognitive dysfunction in older adults[65,66]. However, recent findings from our previous study showed that cognitively impaired females from the ADNI had higher PVS volume fraction in the white matter compared to males, and the PVS changes in the anterosuperior medial temporal lobe in persons with mild cognitive impairment were associated with tau uptake[12]. These findings encourage more research on the effect of the PVS burden on cognition.

The presence of WMH was evaluated through the quality control process by trained PVS analysts, and WMH was not excluded using Fluid Attenuated Inversion Recovery (FLAIR) sequences since FLAIR was not part of the HCPA dataset. However, the effect of WMH on PVS segmentation in our previous study was evaluated in a random sample of 200 participants from the entire HCP datasets (100 HCP-Aging, 50 HCP-Young Adults, and 50 HCP-Developing participants), but no significant correlation was observed[8]. Therefore, the altered PVS structure in this study cannot be attributed to the presence of WMH in the PVS segmentation method.

As a mean of removing metabolic waste from the brain, the glymphatic system has gained increasing attention in recent years[67,68]. There is also evidence that this clearance mechanism is cyclic, notably more prominent during non-rapid eye movement (NREM) sleep than during waking hours[68]. With age, sleep fragmentation increases, which causes less NREM sleep to occur[51]. In this sense, sleep deprivation may contribute to waste protein accumulation in the brain. In the aging population, occurrence of sleep disturbances during NREM happens many years before the clinical diagnosis of AD. NREM sleep disruption has also been linked to the aggregated amyloid and tau proteins associated with Alzheimer's disease, and sleep disruption in normal older adults increases risk of AD[67,69]. In our study of PVS in a healthy aging cohort, we established a baseline against which pathological PVS changes can be compared against, thus helping us gain a better understanding of how sleep affects PVS in healthy adults and in those with neurodegenerative diseases.

There are three advancements in this study compared to previous research in this area. First, we calculated the actual PVS volume rather than the traditional PVS five-point rating[70]. The rating system is based on counting the visible PVSs in the ROI region and rating individuals accordingly; thus, this technique is only useful for the large PVSs, and it may miss subtle important information of global PVS alteration. Second, we analyzed data from a large healthy cohort study, thereby providing a normative map. Third, PSQI included several broad domains of sleep: sleep duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, sleep quality, and sleep medication use. These measures cover many different sleep problems, mostly related to insomnia, and sleep quality. In addition, some studies also suggest that removing sleep medication and daytime dysfunction can help achieve more reliable results from the PSQI questionnaire[71,72]. Therefore, we used individual aspects of the PSQI questionnaire in this study to investigate if there were associations between a range of sleep behaviors and PVS.

However, there are also certain limitations to this study. First, the PSQI is a self-reported questionnaire; thus, biases might exist in the responses to the PSQI items[73,74]. Objective validation of the PSQI measures could include polysomnography in future studies to ensure validity and precision in sleep findings. Second, the MoCA and NIH toolbox working memory questionnaires used in this study are not thorough assessments of memory performance; therefore, more extensive cognitive measurements are needed. Nevertheless, these questionnaires were the only data available in the HCP-Aging dataset. Since this study is a cross-sectional study, the direction of causation of the reported associations are hard to assess; therefore, additional tests and longitudinal assessments are warranted to structure causal relationships in future studies. Exploring other biophysical characteristics of PVS, such as diffusion[75,76], and its relationship with sleep quality is another future direction to this study.

In conclusion, we investigated the relationship between the PVS volume fraction and sleep measures in the HCP-Aging healthy cohort. The effect of sleep on the PVS volume fraction varied in different ages. PVS volume fraction differed by race/ethnicity. In the future, this study could provide a baseline of comparison for the relationship between physiological changes in PVS and sleep behavior. Our study advances our understanding on the role of sleep and brain clearance in cognitively healthy aging adults

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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HCP-Aging:

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Highlights

- The link between sleep and PVS volume fraction varies by age.
- Older adults who had better sleep quality and sleep efficiency have larger BG-PVS.
- BMI mediated the effect of sleep on BG-PVS in the whole cognitively healthy cohort.
- There are differences in PVS volume fraction across racial/ethnic cohorts.

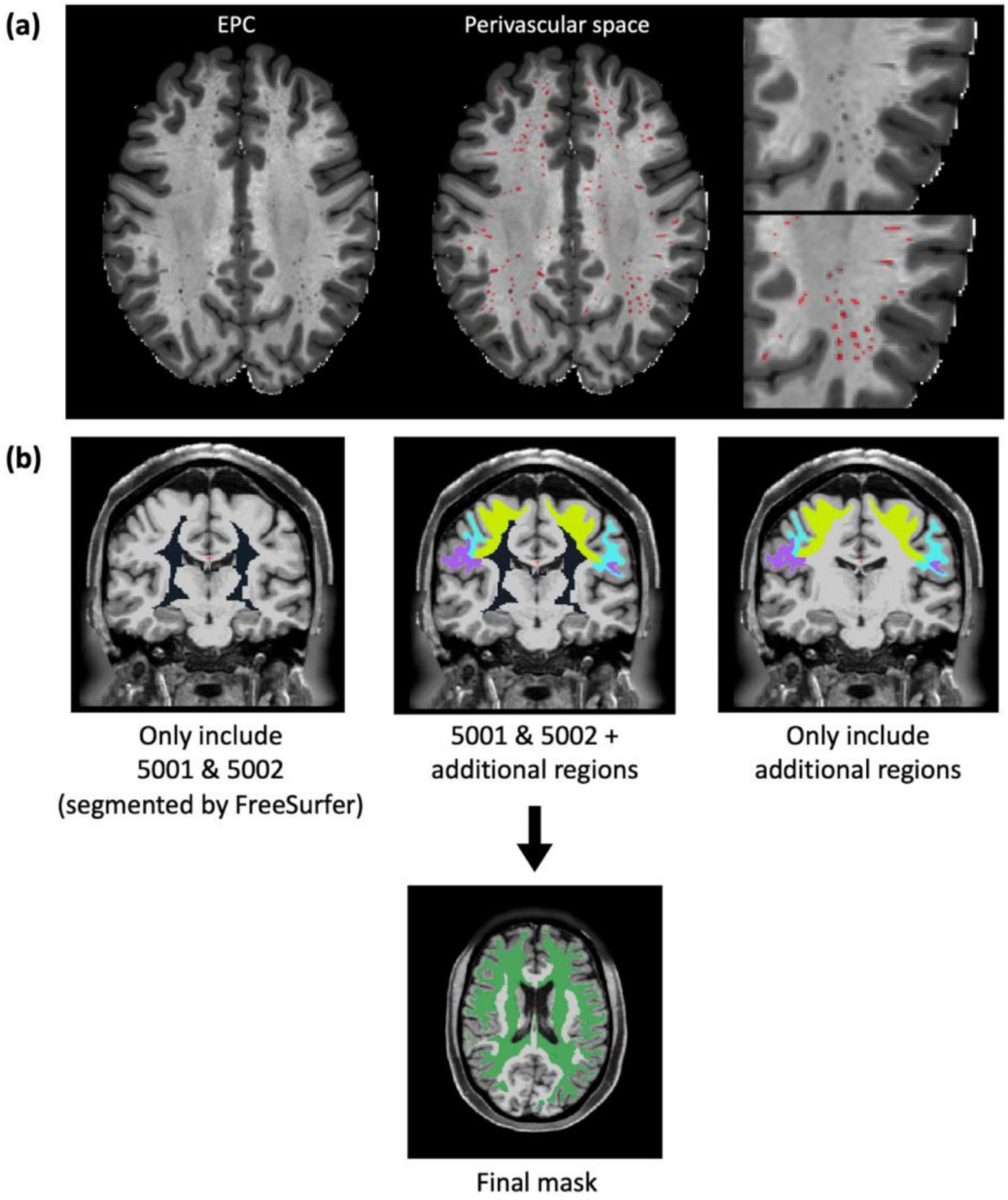


Figure 1. Examples of perivascular space (PVS) and centrum semiovale (CSO) mask.
(a) Enhanced PVS contrast (EPC) image overlaps with the PVS mask (red area). **(b)** Mask of the centrum semiovale (CSO).

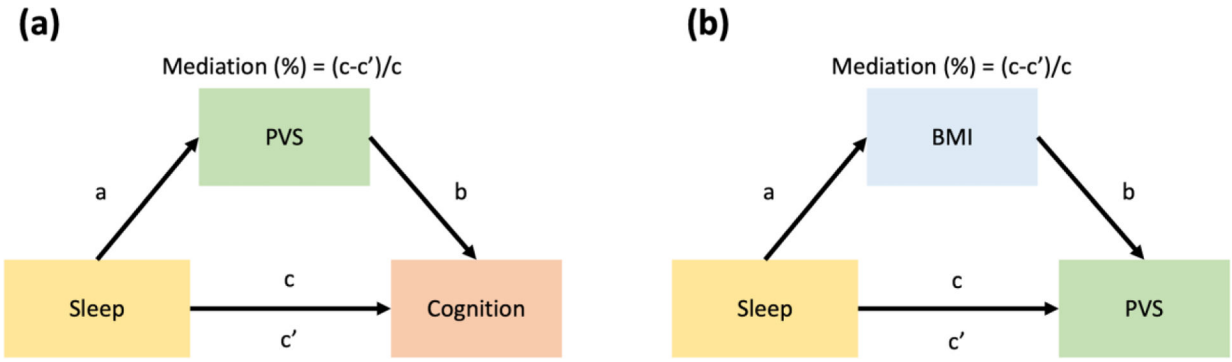


Figure 2. The simple mediation model was conducted in this study.

In **(a),** cognitive performance is regarded as a dependent variable, sleep measurement is regarded as an independent variable, and PVS volume fraction is regarded as a mediator; In **(b)**, PVS volume fraction is considered the dependent variable, sleep measurement is considered an independent variable, and BMI is considered the mediator. Mediation (%) = (c-c')/c.

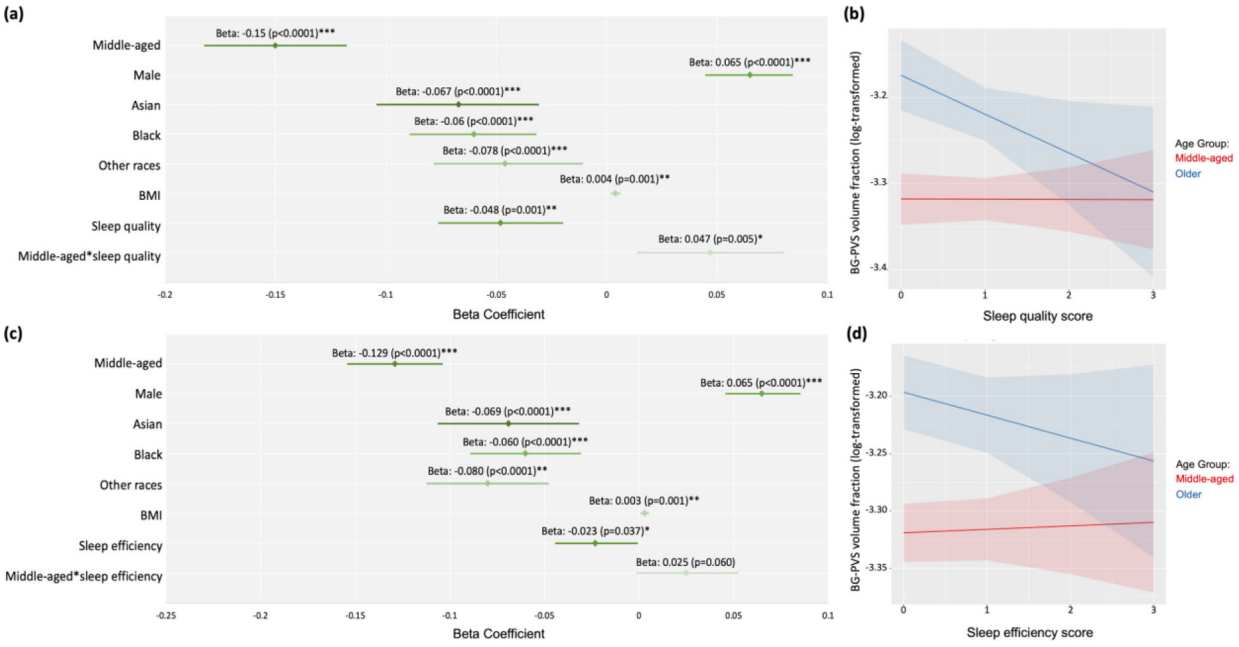
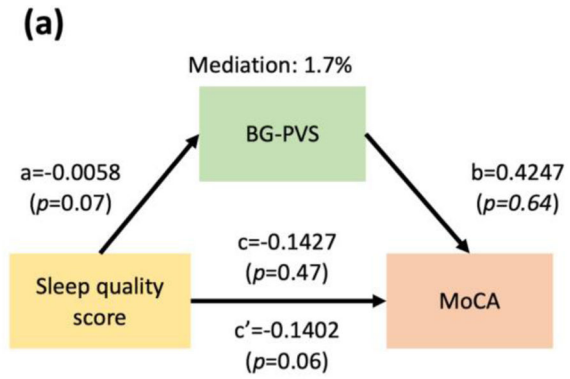
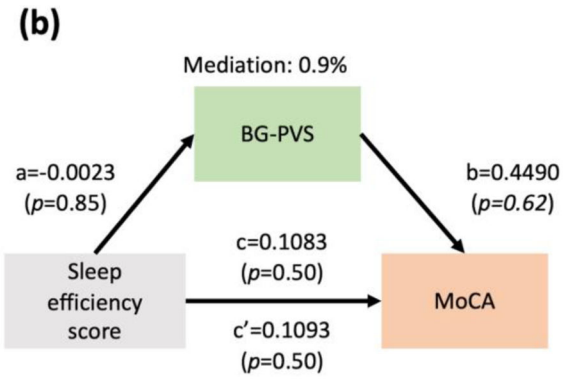


Figure 3. Forest plots illustrating the association between the PVS volume fraction and sleep measures in healthy participants.

(a) Multiple linear regression analysis was conducted to investigate the relationship between the PVS volume fraction in basal ganglia (BG) and sleep quality score. **(b)** The interaction between age groups and sleep quality. **(c)** The relationship between the PVS volume fraction in BG and sleep efficiency score. **(d)** The interaction between age groups and sleep efficiency. The red line represents the middle-aged group (mean of age= 49.50 years old); the blue line represents the older age group (mean of age= 70.19 years old). Significant *p<0.05; **p<0.001; ***p<0.0001



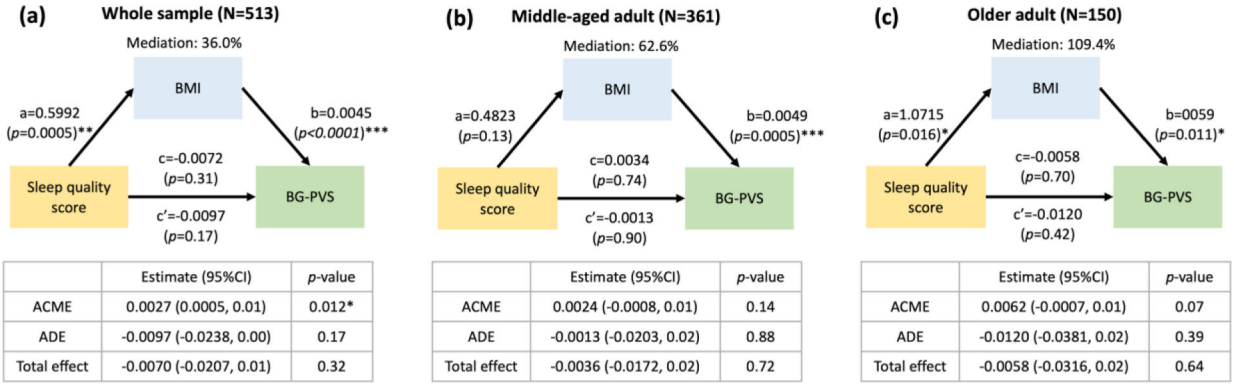
	Estimate (95%CI)	*p*-value
ACME	-0.0024 (-0.0268, 0.03)	0.94
ADE	-0.1403 (-0.4938, 0.22)	0.42
Total effect	-0.1427 (-0.4886, 0.22)	0.42



	Estimate (95%CI)	*p*-value
ACME	-0.0010 (-0.0270, 0.02)	0.83
ADE	0.1093 (-0.1977, 0.41)	0.52
Total effect	0.1083 (-0.2026, 0.41)	0.53

Figure 4. Demonstration of the mediation analysis of the perivascular space (PVS) in the basal ganglia (BG), sleep quality/efficiency and cognitive performance in the older participants.

(a) There is no mediating effect of BG-PVS volume fraction on the association between sleep quality and the Montreal Cognitive Assessment (MoCA) score. **(b)** There is no mediating effect of BG-PVS volume fraction on the association between sleep efficiency and Montreal Cognitive Assessment (MoCA) score. Mediation (%) = (c-c')/c. ACME: Average Causal Mediated Effect; ADE: Average Direct Effect. Significant *p<0.05



	Estimate (95%CI)	*p*-value
ACME	0.0027 (0.0005, 0.01)	0.012*
ADE	-0.0097 (-0.0238, 0.00)	0.17
Total effect	-0.0070 (-0.0207, 0.01)	0.32

	Estimate (95%CI)	*p*-value
ACME	0.0024 (-0.0008, 0.01)	0.14
ADE	-0.0013 (-0.0203, 0.02)	0.88
Total effect	-0.0036 (-0.0172, 0.02)	0.72

	Estimate (95%CI)	*p*-value
ACME	0.0062 (-0.0007, 0.01)	0.07
ADE	-0.0120 (-0.0381, 0.02)	0.39
Total effect	-0.0058 (-0.0316, 0.02)	0.64

Figure 5. Demonstration of the mediation analysis of the perivascular space (PVS) in the basal ganglia (BG), sleep quality and BMI in the whole sample (N=513), middle-aged participants (N=363) and older participants (N=150).

(a) The relationship between sleep quality score, body mass index (BMI), and BG-PVS volume fraction in the whole sample. It depicted the significant indirect effect of sleep quality on the BG-PVS volume fraction through the BMI in whole sample. **(b)** In the middle-aged group, there is no mediation effect of sleep quality on BG-PVS volume fraction through BMI in the middle-aged cohort. The BMI is directly positively associated with BG-PVS volume fraction. **(c)** In the older age group, the sleep quality is significantly associated with BMI. BMI is significantly associated with PVS. But, the effect of sleep quality on PVS was not mediated through BMI significantly.. The direct effect of the path is the coefficient a, b, and c. The indirect effect is the coefficient c'. Mediation (%) = (c-c')/c. ACME: Average Causal Mediated Effect; ADE: Average Direct Effect. Significant *p<0.05

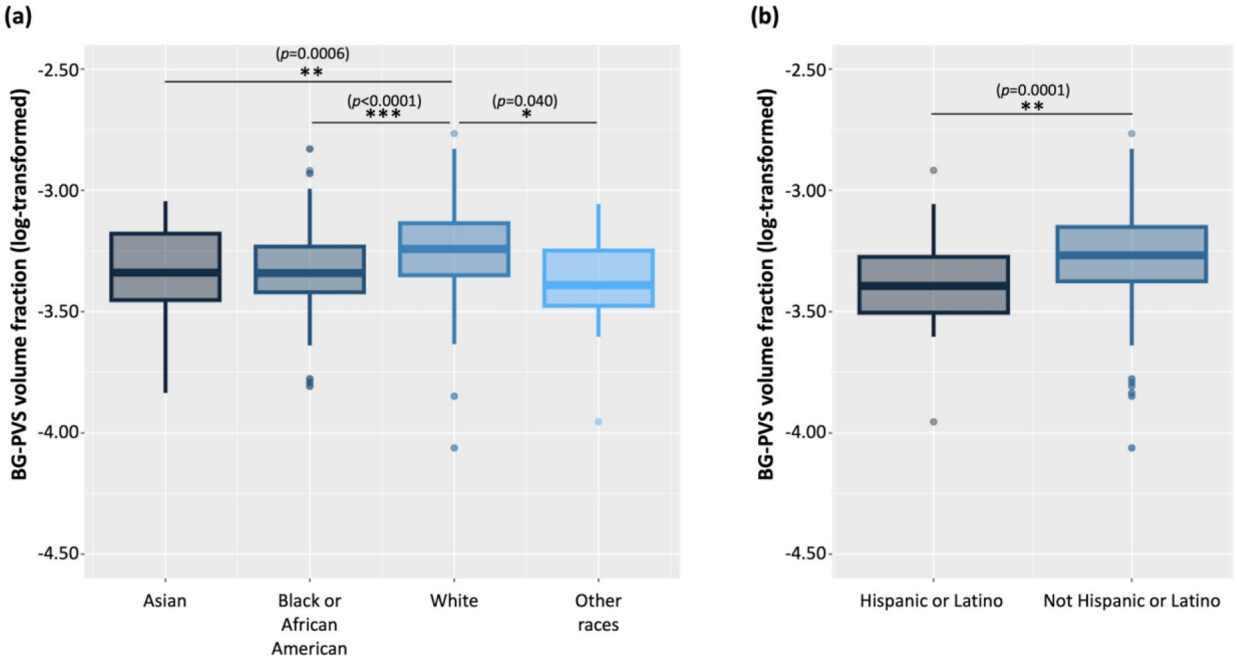


Figure 6. The perivascular space (PVS) in the basal ganglia (BG) by race/ethnicity.

(a) Asians had significantly smaller BG-PVS volume fraction than Whites. African Americans had significantly smaller BG-PVS volume fraction than Whites. Participants of other races had significantly smaller BG-PVS volume fraction than Whites. **(b)** Hispanic or Latino participants had smaller BG-PVS than non-Hispanic persons. Significant *p<0.05; **p<0.001; ***p<0.0001

Table 1.

Demographic information of the study cohort.

	Middle-aged Adult 36–65 years old (N=363)	Older Adult Above 65 years old (N=150)	p-value
Age	49.5±8.3	73.9±6.2	<0.0001***
Sex (M/F)	147(40%)/216(60%)	68(45%)/82(55%)	0.031*
BMI (kg/ m^2)	27.12±4.95	26.68+4.47	0.33
Race (Asian/Black/White/Other groups)	33(9%)/69(19%)/207(57%)/53(14%)	9(6%)/6(4%)/132(88%)/3(2%)	
Ethnicity (Hispanic or Latino/ Non-)	46(13%)/317(87%)	1(0.6%)/149(99.4%)	
Intracranial Volume	1463660.96±201010.38	1554716.80±169200.00	<0.0001***
Region of Interest			
BG Volume (mm^3)	39257.30±3539.08	36282.97±3541.92	<0.0001***
CSO Volume (mm^3)	251966.27±31961.19	233757.27±31058.74	<0.0001***
PVS			
BG-PVS Volume (mm^3)	758.78±331.18	1085.95±445.37	<0.0001***
CSO-PVS Volume (mm^3)	6022.79±2792.79	7090.70±2613.59	<0.0001***
PSQI			
PSQI Total Score	4.56±2.69	4.81±2.72	0.34
Sleep Efficiency Score	0.43±0.75	0.47±0.81	0.57
Sleep Quality Score	0.82±0.69	0.70±0.61	0.046*
Sleep Latency Score	0.80±0.85	0.86±0.83	0.49
Duration of Sleep (h)	6.78±1.04	7.03±1.08	0.017*
Time in bed (h)	8.45±3.17	8.43±2.45	0.95
Daytime dysfunction	0.47±0.50	0.53±0.50	0.25
Sleep medication	0.42±0.91	0.71±1.15	0.003*
Cognitive performance			
MoCA score	26.77±2.35	26.19±2.38	0.012*
NIH toolbox Working Memory score	102.93±14.45	106.81±13.11	0.005*

Data are presented as mean value ± standard deviation (SD). Mann-Whitney U, and t-tests were used to compare PVS volume fraction and sleep measurements between individuals of different ages. The ANOVA test was applied to compare PVS volume fraction between different races. BMI: body mass index; BG: basal ganglia; CSO: centrum semiovale; MoCA: Montreal Cognitive Assessment; PSQI: Pittsburgh Sleep Quality Index; PVS: perivascular space.

Significant *p<0.05; ***p<0.0001