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Enlarged basal ganglia perivascular spaces and sleep parameters. A population-based study

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ABSTRACT

Objective: Perivascular spaces (PVS) are involved in mechanisms of brain interstitial fluid and metabolic waste clearance. Since most of this clearance occurs during sleep, it is plausible that sleep-related disorders favor PVS dilatation. Knowledge on the association between enlarged basal ganglia (BG) PVS and sleep disorders is limited. Here, we aimed to assess the association between sleep parameters and enlarged BG-PVS in older adults.

Patients and methods: Atahualpa residents aged ≥60 years were interviewed with the Pittsburgh sleep quality index and underwent MRI for identification of enlarged BG-PVS and other neuroimaging signatures of cerebral small vessel disease. Then, a representative random sample of the study population underwent a single-night polysomnography (PSG). Using logistic regression models, we evaluated whether sleep quality, sleep efficiency and the apnea-hypopnea index (AHI) associate with enlarged BG-PVS, after adjusting for demographics, cardiovascular risk factors, neuroimaging signatures of cerebral small vessel disease and other relevant confounders.

Results: The association between sleep quality and enlarged BG-PVS, assessed in 338 individuals, was significant in the univariate model, but the significance was taken away by the effect of confounders. The association between PSG parameters and enlarged BG-PVS was assessed in a random sample of 97 individuals. Logistic regression models showed a significant association between poor sleep efficiency and enlarged BG-PVS ($p = 0.045$). In contrast, there was no association between the AHI and BG-PVS.

Conclusion: Poor sleep efficiency is independently associated with enlarged BG-PVS, suggesting that sleep may influence structural changes in these fluid-filled cavities.

1. Introduction

Perivascular spaces (PVS) – also known as Virchow-Robin spaces – are fluid-filled cavities that surround small perforating vessels in their course from the subarachnoid space through the brain parenchyma [1]. These structures, most often located in the basal ganglia (BG) and centrum semiovale (CSO), are thought to be involved in mechanisms of brain interstitial fluid and metabolic waste clearance, and have been referred as a proto-lymphatic or glymphatic system [2,3].

It is possible that conditions disturbing physiological mechanisms of clearance modify PVS causing their dilatation, and hence, their visualization on neuroimaging studies, particularly on high-resolution MRI. Several studies have shown diverse correlates for enlarged PVS according to their location, suggesting different processes involved in their occurrence [4]. CSO-PVS have been associated with cerebral amyloid angiopathy and superficial siderosis [5]. On the other hand, there is increasing evidence linking the presence of enlarged BG-PVS with neuroimaging signatures of cerebral small vessel disease (SVD), microvascular damage of other organs, intracranial atherosclerosis, and some inflammatory conditions [6–11].

Some studies have suggested that interstitial fluid and metabolic waste drainage of the brain occurs during sleep [3,12]. Therefore, it is conceivable that sleep-related disorders alter these clearance mechanisms, thus favoring enlargement of PVS. In this view, an inverse relationship between some polysomnography (PSG)-derived sleep parameters and enlarged BG-PVS was found in a recent study involving 26 patients with stroke or vascular risk factors [13]. To the best of our knowledge, this is the only clinical study specifically addressing such association. Using the Atahualpa Project cohort, we aimed to assess the association between enlarged BG-PVS with sleep-related symptoms and

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PSG-derived sleep parameters in a population of stroke-free community-dwelling older adults.

2. Patients and methods

2.1. Study population

Atahualpa is a rural village located in coastal Ecuador, where previous epidemiological studies on sleep-related symptoms have been conducted [14–16]. As detailed elsewhere, more than 95% of the population belongs to the Ecuadorian native/Mestizo ethnic group, and their lifestyle, socio-economic status and dietary habits are homogeneous; these consistencies reduce the risk of unexpected confounders at the time of analyses [17]. In addition, individuals are exposed to 12 daily hours of sunlight all over the year, shift working is limited and nighttime light pollution is scarce, providing an optimal scenario for studying sleep-related symptoms.

2.2. Study design

Using a population-based cross-sectional study design, we aimed to assess the relationship between sleep quality and enlarged BG-PVS in stroke-free individuals aged ≥60 years enrolled in the Atahualpa Project Neuroimaging Substudy. Thereafter, we investigated the relationship between PSG-derived sleep parameters and enlarged BG-PVS in the subset of individuals who also underwent this diagnostic test. For all analyses, the dependent variable was the presence of enlarged BG-PVS. The Institutional Review Board of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867) approved the protocol and the informed consent forms that individuals must sign before enrollment.

2.3. Neuroimaging protocol

Exams were performed by the use of a Philips Intera 1.5 T MRI scanner (Philips Medical Systems, Eindhoven, the Netherlands). MRI included two-dimensional multi-slice turbo spin echo T1-weighted, fluid attenuated inversion recovery (FLAIR), T2-weighted, and gradient-echo sequences in the axial plane, as well as a T1-weighted sequence oriented in the sagittal plane; slice thickness was 5 mm with 1 mm gap between slices. Interest on MRI readings focused on the presence of neuroimaging signatures of cerebral SVD. In particular, white matter hyperintensities (WMH) of presumed vascular origin were defined as lesions appearing hyperintense on T2-weighted images that remained bright on FLAIR (without cavitation) and graded according to the modified Fazekas scale [18]. Cerebral microbleeds (CMB) were identified and rated according to the microbleed anatomical rating scale [19]; for this study, only CMB located deep in the brain were considered. Lacunar infarcts were defined as fluid-filled cavities measuring 3–15 mm located in the territory of a perforating arteriole [20]. Enlarged basal ganglia perivascular spaces (BG-PVS) were defined as small (< 3 mm) structures of CSF intensity – assessed on the T2-weighted sequence – that followed the orientation of perforating arteries (Fig. 1), and rated as abnormal if > 10 of these lesions were present in a single slice in one side of the brain (we used the BG slice with the highest number in one side) [6]. All MRIs were independently read by two raters blinded to clinical information. As previously described, Kappa coefficients for interrater agreement were high for all the neuroimaging signatures of interest, and discrepancies were resolved by consensus [21].

2.4. Sleep quality assessment

Sleep quality was assessed by means of the Pittsburgh Sleep Quality Index (PSQI), as previously detailed [14]. The PSQI discriminates between "good" and "poor" sleepers. The PSQI consists of 19 items grouped into seven components, each weighted on a 0–3 scale, for a total score of 21, with a score of ≥6 indicating a poor sleep quality. Components include assessment of sleep duration, sleep disturbances, sleep latency, daytime dysfunction due to sleepiness, sleep efficiency, overall sleep quality, and medications needed to sleep.

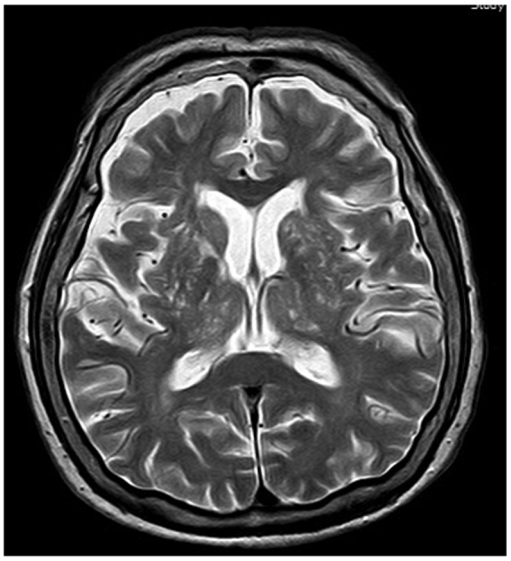

Fig. 1. T2-weighted MRI of a study participant with massively enlarged basal ganglia perivascular spaces bilaterally.

2.5. Polysomnography

As described elsewhere [16], subjects undergoing PSG comprised a representative sample of individuals having an MRI, which were selected by the use of the Random Integer Generator (https://www.random.org/integers/). For this selection, participants were ordered according to their unique 7-digit code used for enrollment in the Atahualpa Project. If a given randomly selected individual did not agree to participate, then, the next on the list was chosen. Consenting individuals were invited to undergo a single-night PSG at the sleep unit of the Atahualpa Project Community Center. Exams were performed with the use of an Embletta® X100™ Comprehensive Portable PSG System (Embla Systems, Inc; Thornton, CO, USA). A board-certified sleep medicine neurologist, blinded to other information, reviewed raw data and interpreted all exams. Sleep efficiency and the apnea/hypopnea index (AHI) data were used for objective assessment of PSG-derived sleep parameters. PSGs were scored based upon recommended by the American Academy of Sleep Medicine (AASM) scoring guidelines [22]. All of the raw data was reviewed in 30 s epochs, as recommended by AASM. Sleep efficiency (SE) was defined as the ratio of total sleep time to time in bed, multiplied by 100.

2.6. Clinical covariates investigated

Demographics, cardiovascular risk factors, edentulism and symptoms of depression were chosen as confounding variables. These relevant confounders were assessed through interviews and procedures previously described in the Atahualpa Project [23–25]. We used the American Heart Association criteria to assess smoking status, physical activity, diet, the body mass index, blood pressure, fasting glucose, and total cholesterol blood levels [26]. Severe edentulism was defined in individuals having less than 10 remaining teeth (a rural dentist performed an oral exam in all cases) [24], and symptoms of depression were assessed by the depression axis of the depression-anxiety-stress-21 scale, a reliable field instrument that measures dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia [25]. To recognize – and exclude – patients with

overt strokes, rural doctors screened all participants with the use of a validated field instrument, and then, certified neurologists confirmed the diagnosis.

2.7. Statistical analysis

Data analyses were carried out by using STATA version 15 (College Station, TX, USA). In univariate analyses, continuous variables were compared by linear models and categorical variables by x^2 or Fisher exact test as appropriate. In order to predict the presence of enlarged BG-PVS by the quality of sleep, we first constructed a logistic regression model adjusted for demographics, cardiovascular risk factors, edentulism, and symptoms of depression. Then, non-significant variables were removed until we obtained the most parsimonious model. In a second step, we included neuroimaging signatures of cerebral SVD and followed the same steps to get the best predictive model by removing non-significant neuroimaging variables. The association between PSG-derived sleep parameters (sleep efficiency and the AHI) and enlarged BG-PVS was investigated by multivariate generalized linear models, using the same steps previously described (removing non-significant clinical variables until the most parsimonious model was obtained, and then, removing non-significant neuroimaging signatures of cerebral SVD until the best predictive model was obtained).

3. Results

Of 437 community-dwelling Atahualpa residents aged ≥60 years identified during door-to-door surveys, 363 (83%) underwent brain MRI and were considered eligible for being included in this study. Reasons for not obtaining MRI included refusal to sign the informed consent (n = 40), severe disability (n = 15), claustrophobia (n = 9), and implanted pacemaker (n = 1); nine additional persons had died between the survey and the invitation. Twenty-five of the 363 persons undergoing MRI were further excluded because neurological examination together with MRI showed an overt stroke, leaving 338 included individuals.

3.1. Sleep quality and enlarged BG-PVS

The association between sleep quality and enlarged BG-PVS was assessed in 338 individuals. Their mean age was 70.7 ± 8 years (median age: 69 years; age range 60–99 years) and 197 (58%) were women. Eight (2%) individuals were current smokers, 15 (4%) had a poor diet, and 24 (7%) had poor physical activity. A body mass index ≥30 kg/m^2 was noticed in 79 (23%) persons, blood pressure ≥140/90 mmHg in 152 (45%), fasting glucose ≥126 mg/dL in 108 (32%), total cholesterol levels ≥240 mg/dL in 43 (13%), severe edentulism in 153 (45%), and symptoms of depression in 38 (11%). Moderate-to-severe WMH were noticed in 71 (21%), silent lacunar infarcts in 33 (10%), deep CMB in 25 (7%), and enlarged BG-PVS in 86 (25%). A total of 108 (32%) had a poor sleep quality (PSQI ≥ 6 points).

Table 1 shows characteristics of participants across categories of PSQI and enlarged BG-PVS. In univariate analyses, increasing age ($p < 0.001$), having blood pressure levels ≥140/90 mmHg ($p = 0.001$), moderate-to-severe WMH ($p < 0.001$), silent lacunar infarcts ($p < 0.001$) and deep CMB ($p = 0.001$) were significantly associated with enlarged BG-PVS. On the other hand, a poor sleep quality was significantly associated with increasing age ($p = 0.003$), poor physical activity ($p < 0.001$), and moderate-to-severe WMH ($p = 0.012$). A univariate logistic model of enlarged BG-PVS (dependent variable) and sleep quality was significant (OR: 1.68; 95% C.I.: 1.01–2.79; $p = 0.045$). However, logistic regression models adjusted for relevant confounders, showed no association between sleep quality and enlarged BG-PVS (Table 2).

3.2. PSG-derived sleep parameters and enlarged BG-PVS

The association between sleep efficiency and the AHI with enlarged BG-PVS was assessed in a random sample of 97 of the 338 individuals included in the previous analysis. As previously described, the original sample included 104/338 (31%) individuals, but poor PSG recordings precluded adequate readings in seven cases [16]. Mean age of the 97 individuals was 72.3 ± 7 years (median age: 72 years) and 63 (65%) were women. Only one (1%) subject was a current smoker, two (2%) had a poor diet, and six (6%) had poor physical activity. A body mass index ≥30 kg/m^2 was noticed in 20 (21%) persons, blood pressure ≥140/90 mmHg in 52 (54%), fasting glucose ≥126 mg/dL in 29 (30%), and total cholesterol levels ≥240 mg/dL in 17 (18%). The covariates edentulism and symptoms of depression were not evaluated in this series due to their lack of association with PSG-derived sleep parameters. Moderate-to-severe WMH were noticed in 25 (26%), silent lacunar infarcts in 22 (23%), deep CMB in 12 (12%), and enlarged BG-PVS in 38 (39%). The mean percentage of sleep efficiency was 75 ± 14.3 (median: 75.2), with 73 (75%) individuals disclosing < 85% of sleep efficiency. Mean AHI was 13.8 ± 14.1 episodes per hour (median: 8.8). Twenty-seven subjects have < 5 episodes per hour, 43 had between 5–15 episodes per hour, and the remaining 27 (28%) had ≥15 episodes per hour; the latter were considered to have moderate-to-severe obstructive sleep apnea. Table 3 shows the characteristics of participants across categories of sleep efficiency and the AHI. As noticed, the only significant difference in univariate analyses was the higher prevalence of moderate-to-severe WMH among individuals with an AHI ≥ 15 episodes per hour (20% versus 41%, $p = 0.036$).

Logistic regression models adjusted for relevant confounders, showed a significant association between poor sleep efficiency and enlarged BG-PVS (Table 4). In contrast, there were no associations between the AHI and BG-PVS, either when the AHI was used as a continuous variable (OR: 1.02; 95% C.I.: 0.98–1.06; $p = 0.342$) or when it was stratified according to the episodes of AHI per hour (OR: 1.40; 95% C.I.: 0.394–4.98; p = 0.601, and OR: 0.64; 95% C.I.: 0.16–2.55; p = 0.525, respectively).

4. Discussion

This population-based study, conducted in community-dwelling older adults living in a remote rural setting, shows dissimilar relationships between sleep-related symptoms and parameters, and the presence of enlarged BG-PVS. The relationship between poor sleep quality and enlarged BG-PVS was significant in the univariate model, but it was lost in multivariate models, suggesting that the significance was progressively taken away by the effect of increasing age and other neuroimaging signatures of cerebral SVD. The odds for this association decreased from 1.68 (95% C.I.: 1.01–2.79) in the univariate model, to 1.26 (95% C.I.: 0.71–2.24) when clinical covariates were included, and to 1.19 (95% C.I.: 0.65–2.19) when moderate-to-severe WMH and lacunar infarcts were added to the model.

Of the two sleep parameters evaluated in PSG, poor sleep efficiency was independently associated with enlarged BG-PVS in the most parsimonious regression model, but the AHI was not. These results are in line with those found by Berezuk et al. [13] in the only study addressing this relationship in humans. The authors studied 26 patients with PSG and 3-D high resolution MRI and found an inverse relationship between sleep efficiency and the volume of BG-PVS, after adjusting for relevant confounders. Results from both the Berezuk's and the present study suggest that inefficient perivascular drainage (leading to abnormal enlargement of these structures) may occur in subjects with a lower percentage of time spent asleep.

The work of Berezuk et al. [13] was criticized due to the characteristics of the study population (a small series of relatively young individuals with stroke or at high risk for stroke), and it was hypothesized that their findings might be just a reflection of an incidental

Table 1
Characteristics of 338 Atahualpa residents aged ≥60 years across categories of enlarged basal ganglia perivascular spaces and sleep quality (univariate analysis).

	Total series (n = 338)	Basal ganglia perivascular spaces			Sleep quality		
		Normal (n = 252)	Enlarged (n = 86)	*p* value	Good (n = 230)	Poor (n = 108)	*p* value
Age, years (mean ± SD)	70.7 ± 8	69 ± 7.2	75.6 ± 8	< 0.001 *	69.8 ± 7	72.6 ± 9.5	0.003 *
Women, n (%)	197 (58)	145 (58)	52 (60)	0.729	131 (57)	66 (61)	0.549
Current smokers, n (%)	8 (2)	8 (3)	0	0.094	5 (2)	3 (3)	0.714
Poor diet, n (%)	15 (4)	12 (5)	3 (3)	0.768	10 (4)	5 (5)	0.863
Poor physical activity, n (%)	24 (7)	15 (6)	9 (10)	0.245	8 (3)	16 (15)	< 0.001 *
Body mass index ≥30 Kg/m^2, n (%)	79 (23)	62 (25)	17 (20)	0.443	50 (22)	29 (27)	0.368
Blood pressure ≥140/90 mmHg, n (%)	152 (45)	100 (40)	52 (60)	0.001 *	98 (43)	54 (50)	0.247
Fasting glucose levels ≥126 mg/dL, n (%)	108 (32)	79 (31)	29 (34)	0.791	68 (30)	40 (37)	0.212
Total cholesterol ≥240 mg/dL, n (%)	43 (13)	29 (12)	14 (16)	0.338	28 (12)	15 (14)	0.791
Severe edentulism, n (%)	153 (45)	109 (43)	44 (51)	0.251	97 (42)	56 (52)	0.121
Symptoms of depression, n (%)	38 (11)	24 (10)	14 (16)	0.130	21 (9)	17 (16)	0.108
Moderate-to-severe WMH, n (%)	71 (21)	29 (12)	42 (49)	< 0.001 *	39 (17)	32 (30)	0.012 *
Silent lacunar infarcts, n (%)	33 (10)	11 (4)	22 (26)	< 0.001 *	22 (10)	11 (10)	1
Deep cerebral microbleeds, n (%)	25 (7)	11 (4)	14 (16)	0.001 *	18 (8)	7 (7)	0.823

WMH: white matter hyperintensities; BG-PVS: basal ganglia perivascular spaces.
* Statistically significant result.

Table 2
Logistic regression models showing the relationship between sleep quality and enlarged basal ganglia perivascular spaces (as the dependent variable). The upper panel shows the model adjusted for demographics, cardiovascular risk factors, edentulism, and symptoms of depression. The lower panel shows the best predictive model after removing non-significant clinical variables and adding significant neuroimaging signatures of cerebral small vessel disease. There was no association between sleep quality and enlarged basal ganglia perivascular spaces.

Enlarged BG-PVS	Odds ratio	95% Confidence Interval	P value
Sleep quality	1.256	0.706–2.235	0.438
Age	0.912	0.880–0.944	< 0.001 *
Sex	1.113	0.629–1.967	0.713
Body mass index	0.921	0.464–1.829	0.814
Physical activity	0.912	0.325–2.558	0.862
Diet	0.661	0.163–2.678	0.562
Blood pressure	1.686	0.971–2.927	0.063
Fasting glucose	0.984	0.549–1.764	0.958
Total cholesterol	1.538	0.719–3.289	0.267
Edentulism	1.055	0.610–1.824	0.849
Symptoms of depression	1.359	0.608–3.039	0.454
Sleep quality	1.190	0.645–2.195	0.577
Age	0.937	0.903–0.971	< 0.001 *
Moderate-to-severe WMH	4.239	2.224–8.079	< 0.001 *
Lacunar infarcts	5.050	2.177–11.716	< 0.001 *

BG-PVS: basal ganglia periventricular spaces; WMH: white matter hyperintensities.
* Statistically significant result.

association between poor sleep and neuroimaging signatures of cerebral SVD, which include enlarged BG-PVS [27]. However, the same results were found in the present study, which evaluated this association in an unbiased population of stroke-free community-dwelling older adults, providing further support to the concept that poor sleep efficiency is associated with enlarged BG-PVS. We did not assess the presence of enlarged CSO-PVS or its association with sleep disorders, and this is a limitation of our study. CSO-PVS were not measured in part because it is complicated to accurately assess the burden of such spaces without the aid of 3D-MRI volumetric analysis, and because the study of Berezuk et al. [13] did not show an independent association between sleep efficiency and enlarged CSO-PVS.

Since our study participants underwent only a single night's PSG recording, which is subject to night-to-night variability and first night effect, we did not focus on sleep architecture, but on global measures of sleep such as sleep efficiency and the AHI. Another limitation of the present study is the cross-sectional design, precluding the assessment of causation. However, biological plausibility make unlikely the occurrence of a reverse causation phenomenon, and persistence of the association after adjustment for WMH, CMB and lacunar infarcts, suggest that the observed relationship is beyond the incidental coexistence of the other neuroimaging signatures of cerebral SVD. Another potential limitation is the inclusion of a highly homogeneous population. Therefore, our findings might not be generalized to other populations. However, region-specific knowledge on the association between sleep disorders and neuroimaging signatures of cerebral SVD are of much value to better understand pathogenetic mechanisms implicated in this association in selected populations. On the other hand, the population-based design with unbiased enrollment of participants, the homogeneous characteristics of Atahualpa residents, and the models constructed to assess the association between sleep-related symptoms and parameters and the presence of enlarged BG-PVS, argue for the strengths of our findings.

Experimental studies focused on the role of poor sleep as responsible for accumulation of β-amyloid and other proteins within the brain, which lead to the development of a cerebral amyloid angiopathy [12]. These results have recently been confirmed in a small series conducted in humans, showing that disturbed sleep increases the amount of β-amyloid in the CSF [28]. Since enlarged CSO-PVS have been associated with cerebral amyloid angiopathy [5], it is plausible to assume that sleep disturbances might favor enlargement of CSO-PVS instead of BG-PVS. However, brain interstitial fluid and metabolic waste clearance may conceivable occur at the BG-PVS level, thus explaining the results of both the Berezuk's and the present study.

Evidence on the association between sleep-related disorders and enlarged BG-PVS is quite preliminary. Further studies, preferable longitudinal, are needed to better understand pathogenetic mechanisms of brain interstitial fluid and metabolic waste clearance in the setting of abnormal sleep, and their consequences on the enlargement of PVS at different anatomical locations.

Conflict of interest

The authors have nothing to disclose.

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Table 3
Characteristics of 97 Atahualpa residents aged ≥60 years across categories of sleep efficiency and the apnea-hypopnea index (univariate analysis).

	Total series (n = 97)	Sleep efficiency			Apnea-Hypopnea index		
		Good (≥85%) (n = 24)	Poor (< 85%) (n = 86)	*p* value	0-14 episodes/hour (n = 70)	≥15 episodes/hour (n = 27)	*p* value
Age, years (mean ± SD)	72.3 ± 7	72.2 ± 8.2	72.3 ± 6.5	0.950	72.3 ± 6.4	72.4 ± 8.3	0.950
Women, n (%)	63 (65)	18 (75)	45 (52)	0.079	47 (67)	16 (59)	0.466
Current smokers, n (%)	1 (1)	0	1 (1)	.. .	1 (1.4)	0	.. .
Poor diet, n (%)	2 (2)	0	2 (2)	.. .	1 (1.4)	1 (4)	0.481
Poor physical activity, n (%)	6 (6)	2 (8)	4 (5)	0,609	3 (4.3)	3 (11)	0.344
Body mass index ≥30 Kg/m^2, n (%)	20 (21)	4 (17)	16 (19)	1	15 (21.4)	5 (19)	0.751
Blood pressure ≥140/90 mmHg, n (%)	52 (54)	11 (46)	41 (48)	0.920	39 (55.7)	13 (48)	0.503
Fasting glucose levels ≥126 mg/dL, n (%)	29 (30)	9 (38)	20 (23)	0.254	19 (27.1)	10 (37)	0.340
Total cholesterol ≥240 mg/dL, n (%)	17 (18)	7 (29)	10 (12)	0.075	12 (17.1)	5 (19)	0.873
Moderate-to-severe WMH, n (%)	25 (26)	8 (33)	17 (20)	0.259	14 (20)	11 (41)	0.036 *
Silent lacunar infarcts, n (%)	22 (23)	7 (29)	15 (17)	0.327	13 (18.6)	9 (33)	0.119
Deep cerebral microbleeds, n (%)	12 (12)	4 (17)	8 (9)	0.291	10 (14.3)	2 (7)	0.501

WMH: white matter hyperintensities; BG-PVS: basal ganglia perivascular spaces.
* Statistically significant result.

Table 4
Logistic regression models showing the relationship between sleep efficiency and enlarged basal ganglia perivascular spaces (as the dependent variable). The upper panel shows the model adjusted for demographics and cardiovascular risk factors. The lower panel shows the best predictive model after removing non-significant clinical variables and adding significant neuroimaging signatures of cerebral small vessel disease. There was a significant association between poor sleep efficiency and enlarged basal ganglia perivascular spaces ($p = 0.045$).

Enlarged BG-PVS	Odds ratio	95% Confidence Interval	P value
Sleep efficiency	1.036	0.999–1.075	0.056
Age	0.904	0.831–0.983	0.018 *
Sex	1.777	0.592–5.336	0.305
Body mass index	0.579	0.147–2.286	0.436
Physical activity	3.182	0.402–25.222	0.273
Blood pressure	0.943	0.352–2.526	0.907
Fasting glucose	1.253	0.435–3.607	0.676
Total cholesterol	6.285	1.659–23.805	0.007 *
Sleep efficiency	1.045	1.000–1.090	0.045 *
Age	0.951	0.869–1.040	0.271
Physical activity	4.440	0.533–36.989	0.168
Total Cholesterol	5.849	0.533–36.989	0.168
Moderate-to-severe WMH	10.232	2.672–39.187	< 0.001 *
Lacunar infarcts	2.840	0.701–11.509	0.144
Deep microbleeds	3.839	0.645–22.854	0.139

BG-PVS: basal ganglia periventricular spaces; WMH: white matter hyperintensities.
* Statistically significant result.

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