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Insomnia, early and late rising are associated with small hippocampal volume and large white matter hyperintensity burden

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Abstract

Background Sleep disturbances have been associated with an increased risk of dementia. The mechanisms remain unclear, although neurodegenerative and vascular pathways are potentially involved. Hence, our study aims to investigate the relationships between several clinical sleep and polysomnographic features and volumes of hippocampus (indicative of neurodegeneration) and white matter hyperintensities (WMH) (reflecting vascular processes).

Methods In this cross-sectional study, 678 participants aged 65–80 from the French population-based ESPRIT cohort with MRI-measured hippocampus and/or WMH volumes were included. Self-reported sleep data were collected at baseline, and 176 participants underwent ambulatory polysomnography (PSG). We performed multivariable logistic regression to assess associations between sleep characteristics and hippocampal and WMH volumes.

Results Participants' median age was 70.7 years (Q1-Q3 = 67.8–74.0), with 52.4% being women. Early (≤ 6 am; odds ratio (OR) = 2.03, 95% confidence interval (CI) = 1.17;3.53) and late (> 8 am; OR = 2.14, 95%CI = 1.33;3.43) rising times were associated with low hippocampal volume. Early rising time (OR = 2.06, 95%CI = 1.24;3.43) and insomnia symptoms (OR = 1.84, 95%CI = 1.18;2.86 for 1 symptom, OR = 1.91, 95%CI = 1.18;3.09 for 2–3 symptoms) were associated with large WMH volume, whereas late bedtime (≥ 11 pm; OR = 0.56, 95%CI = 0.39;0.80) was associated with low WMH volume. Based on PSG data, higher rapid-eye movement (REM) sleep percentage (OR = 0.70, 95%CI = 0.50;0.96) was associated with low WMH volume, with similar trends for long sleep bouts duration, N3 and REM sleep durations ($p = 0.05$ to 0.07). Conversely, higher N2 sleep percentage (OR = 1.69, 95%CI = 1.09;2.62), longer NREM sleep bouts (OR = 1.46, 95%CI = 1.02;2.09), and higher periodic leg movements index (OR = 1.55, 95%CI = 1.02;2.26) were associated with large WMH volume. However, no PSG parameter associations remained after false discovery rate correction.

Conclusions Distinct associations between sleep characteristics and hippocampal and WMH volumes were observed, highlighting the important relationships between sleep, sleep timing and brain structure.

Keywords Hippocampus, White matter hyperintensities, MRI, Sleep architecture, Sleep duration, Polysomnography, Aging

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Background

Sleep is a complex physiological process essential for maintaining optimal cognitive health across the lifespan. Disturbances in sleep have been consistently linked to poor cognitive function and an increased risk of developing Alzheimer's disease and related dementias (AD/ADRD) [1]. However, the mechanisms underlying these associations remain unclear, although neurodegenerative and vascular pathways are potentially involved. As subjects advance in age, the complex interplay between sleep patterns and brain structure becomes a focus of investigation, with implications for understanding neurodegenerative processes and cerebrovascular health.

The hippocampus, which plays an important and active role in memory consolidation during sleep, presents alterations in the early stages of neurodegenerative diseases such as in AD [2]. Notably, hippocampal atrophy is a hallmark of neurodegeneration, particularly in AD, and is strongly associated with cognitive decline and disease progression [3–5]. While hippocampal atrophy is also observed in other types of dementia, such as vascular dementia, it tends to be less severe than in AD [3, 6]. Poor sleep quality has been associated with low hippocampal volumes in older adults [7, 8], along with a progressive decline in hippocampal volume over time in subjects aged 18 years and older [9]. Studies have also reported lower hippocampal volumes with insomnia [10, 11], obstructive sleep apnea (OSA) [12], periodic limb movement disorder (PLM) [13], and excessive daytime sleepiness (EDS) [14]. However, other studies have failed to replicate these findings [15–18].

White matter hyperintensity (WMH) burden that reflect demyelination and axonal loss is often use as a proxy for cerebrovascular disease and is considered as the primary pathology of vascular dementia, but may also relate to AD pathology [19–21]. A meta-analysis showed that WMH lesions were associated with a 25% increased risk of AD and a 73% increased risk of vascular dementia [22]. As an intermediate marker of cerebrovascular risk, WMH burden is a well-established contributor to cognitive decline and dementia in aging populations [21, 23]. Sleep disturbances may contribute to the development of WMH, through mechanisms involving impaired cerebral blood flow and inflammation. A relationship between sleep-disordered breathing (SDB) and WMH has been reported in moderate to severe OSA [24]. However, the associations between global WMH and other sleep-related features remained understudied and results are often inconsistent [13, 18, 25–31].

To date, most sleep and neuroimaging research has produced variable results, often using small study samples, relying only on self-reported sleep data, lacking adjustments for important confounders, and focusing on clinical populations. Further investigations within the general population are therefore needed using both self-reported and polysomnographic (PSG) data. Moreover, given the mixed results in the literature and the fact that sleep disturbances are rarely isolated but instead interact in complex ways [32], an exploratory approach is essential to capture the full range of potential associations between sleep characteristics and markers of neurodegeneration and cerebrovascular disease. The selection of sleep parameters should therefore be guided by evidence suggesting that sleep architecture (e.g., slow-wave sleep, rapid-eye movement (REM) sleep), sleep fragmentation (e.g., arousals, wake after sleep onset, sleep bouts), sleep quality (e.g., sleep efficiency, sleep latency, insomnia symptoms), sleep patterns (e.g. sleep duration, napping, time in bed), and sleep-related breathing disturbances (e.g., apnea-hypopnea index, O2 desaturation) play critical roles in brain health [33–35]. Clarifying the relationships between multiple sleep characteristics and two early markers of neurodegeneration and vascular processes might improve our understanding of the links between sleep and cognition.

To address these gaps, this study investigates the associations between both self-reported sleep characteristics and PSG features with the volumes of hippocampus and WMH burden within a large community-dwelling sample of older adults considering numerous important confounders. Given the heterogeneity of previous findings, our study aims to identify the most relevant sleep-related factors associated with early markers of dementia, with potential implications for early intervention strategies to preserve cognitive health in aging populations.

Methods

Study population

Data were obtained from the ESPRIT study, a French ongoing prospective cohort of non-institutionalized participants aged 65 years or older, randomly selected from the electoral rolls of Montpellier district, between 1999 and 2001 [36]. Of the participants initially recruited, only those aged between 65 and 80 years were invited for an MRI brain scan. A total of 760 participants were randomly selected for the imaging study, of whom 725 participants had measurements of hippocampus and/or global WMH volume at baseline.

Baseline magnetic resonance imaging (MRI) acquisition and data

Estimation of hippocampus and intracranial volumes

At baseline (1999–2001), a 1.5T GE Signa Imaging system (General Electric Medical Systems, Milwaukee, Wisconsin) was used to acquire a contiguous anterior commissure-posterior commissure, aligned, axial inversion recovery-prepared, spoiled gradient recalled, T1-weighed sequence for volumetric estimations

(TR = 12, TE = 2.8, IT = 6000, matrix, size = 256 × 256, pixel spacing = 0.9375 × 0.9375 mm, NEX = 1, slice thickness = 1.0 mm). Slices were then converted to be isotropic (0.9375 mm3) and re-sliced to 1.00 mm3. Hippocampus regions of interest were manually outlined on consecutive coronal slices and verified from axial and sagittal orientations [37]. Hippocampus outlines were traced by two trained researchers blind to the study hypotheses, group assignment and subjects' identity. The two researchers each retraced five MRI images - which were randomly selected among the images previously traced - and five images which belonged to the group previously traced by the other researcher, to assess the reliability of the hippocampus measurements. The coefficients showed excellent agreement (0.94 for inter- and 0.94 and 0.97 for intra-class correlations (one for each researcher)). Hippocampal volume was categorized into two groups according to the tertiles of the whole sample to facilitate interpretation, enhance clinical relevance, and ensure sufficient participants per group in analyses with sleep metrics: the at-risk tertile, representing low volume (< 5.4 cm^3), and the other two tertiles corresponding to moderate/large volume (≥ 5.4 cm^3). Intracranial volume (sum of gray matter, white matter, and cerebrospinal fluid volumes) was computed for each subject using the segment m-file in SPM5 (Wellcome Department of Cognitive Neurology, London, United Kingdom). All outputs were manually inspected to ensure accurate and valid data.

Estimation of WMH volume

At baseline (1999–2001), MRI structural imaging was carried out by transversal fast multislice double echo T2-weighted 2D axial acquisition (TR = 4400ms, TE1 and TE2 = 16ms and 98ms, slice thickness = 4 mm, gap = 0.4 mm, matrix = 256 × 256, inplane resolution = 0.98 × 0.98mm2) that covered the whole brain. Global WMH volume was estimated using a semi-automatic method at baseline [38, 39]. Briefly, supratentorial areas that appeared hyperintense on the T2-weighted sequences were segmented with an intensity threshold using MRIcro software [40]. A first layer of region of interest (ROIs) corresponding to WMH was created by using a semi-automated technique based on intensity thresholding. A second layer of ROIs was then manually outlined on each slide by roughly contouring all WMH. The intersection between the first and second steps defined the WMH areas and volume was then manually inspected and automatic WMH volume obtained. An experienced reader blind to the outcomes examined all scans. A neurologist examined 80 randomly chosen scans to assess the inter-rater reliability. The inter-reader and intra-reader, intra-class correlation coefficients showed good to excellent agreement (0.79 and 0.95 respectively). Global WMH volume was categorized into two groups: the at-risk tertile (i.e., 3rd tertile) vs. the other two (i.e., 1st and 2nd tertiles)), corresponding to large (> 1.6 cm^3) and moderate/low (≤ 1.6 cm^3) volumes of the whole sample to aid interpretation and enhance clinical relevance as previously described [41].

Assessment of sleep characteristics

Baseline self-reported data

At baseline (1999–2001), each participant completed a sleep questionnaire about several conditions at time of study. Self-reported sleep data were described in more details elsewhere [42]. Briefly, nighttime sleep duration was categorized as short (≤ 6 h), normal (]6;9[) and long (≥ 9). Napping was classified into three categories: none (no naps); infrequent or short duration (< 3 times/week or < 30 min/day); regular and long duration (≥ 3 times/week and ≥ 30 min/day). Bedtime was categorized as: ≤9;]9–11[; ≥11 pm and rising time as: ≤6;]6–8]; >8 am, in alignment with prior work [42]. Time in bed was estimated by the difference between rising time and bedtime, and used to define sleep efficiency which was calculated by dividing the estimated nighttime sleep duration by the time in bed multiplicate by 100. A good sleep efficiency was considered to be 85% or higher. EDS was assessed by the Epworth Sleepiness Scale, with a score > 10 indicating clinically significant EDS [43]. Sleep satisfaction and insomnia symptoms (e.g., difficulty initiating sleep, maintaining sleep and early morning awakening) were assessed using binary questions (Yes/No). The number of insomnia symptoms was examined as follows: 0;1;2–3 to investigate a potential dose-response effect.

Polysomnography data

In a subsample (n = 390), participants underwent an ambulatory PSG between 2001 and 2010 on a voluntary basis. Participant selection was not influenced by the presence of sleep problems. Among them, 176 participants had both PSG and MRI examinations (median between the two examinations = 9.8 years (Q1-Q3 = 9.4–10.3)). PSG recordings took place in the participant's home using the Deltamed (Natus) coherence system which includes five electroencephalography leads, right and left electro-oculograms, electromyography of chin and tibialis anterior muscles, electrocardiogram, nasal cannula/pressure transducer, mouth thermistor, chest and abdominal bands, body position and pulse oximeter. Sleep characteristics were scored manually by sleep experts according to standard criteria [44–46]. Main exposures of interest consisted in nighttime sleep duration, duration and percentage of sleep in Stage 1 (N1), Stage 2 (N2), Stage 3 (N3), and REM, sleep efficiency, sleep latency, wake after sleep onset (WASO), apnea-hypopnea index (AHI), O2 desaturation index > 3%, index of periodic limb movements of sleep (iPLMS), and sleep

bouts duration. Sleep bouts are less standard metrics, they correspond to any continuous sequence of sleep epochs comprised between two wake epochs and defined here as the median duration of all sleep bouts for each participant. Sleep bouts in sleep, non-rapid eye movement (NREM) sleep, and REM sleep independently were analyzed. Each PSG parameter was studied as a continuously variable.

Baseline covariates

Age, sex, and educational level (≤ primary/> primary) were assessed through a standardized interview. A cardiovascular health score was defined to evaluate the level of cardiovascular health at baseline as described previously [47]. Briefly, it was constructed based on the American Heart Association metrics for ascertainment of cardiovascular health status: smoking, physical activity, diet, body mass index (BMI), total cholesterol, blood pressure and fasting plasma glucose [48]. It was calculated by assigning 0 point for each metric at poor level, 1 point for each metric at intermediate level, and 2 points for each metric at recommended optimal level (total score range, 0–14). Others behavioral and vascular risk factors included alcohol consumption (< 12 g/day; [12;36[; ≥36 g of ethanol per day) and self-reported history of cardiovascular diseases (i.e., angina pectoris, myocardial infarction, cardiovascular surgery, and arteritis). Apolipoprotein e-ε4 (APOE ε4) was genotyped and defined as the presence of at least one ε4 allele. Depressive status was defined as a score ≥ 16-point on the Center for Epidemiological Studies-Depression (CES-D) scale or current antidepressant treatment. Prescribed medications during the preceding month were checked by the interviewer and coded using the World Health Organization Anatomical Therapeutic Chemical classification system. Sleeping pills consisted in benzodiazepines (BZD), benzodiazepines-like compounds, barbiturates, antihistaminic drugs, neuroleptics, and sedative antidepressants.

Statistical analyses

Demographic and clinical characteristics were compared between participants with (i) low and moderate/large hippocampus volume and (ii) large and moderate/low global WMH volume using crude logistic regression models. Multivariable logistic regression models were then performed to examine the associations between sleep variables (self-reported and PSG data) and volumes of hippocampus and global WMH. Covariates were selected based on the literature and univariable analysis ($p < 0.15$). Models were minimally adjusted for sex, age, educational level, presence of APOE ε4, and intracranial volume (Model 1). Supplementary models were further adjusted for behavioral and vascular risk factors variables (Model 2), and depressive status (Model 3) or sleeping pills (Model 4). Results were expressed as odds ratio (OR) with 95% confidence intervals (CI). To account for the multiple tests examined, significance levels were adjusted using the false discovery rate (FDR) method [49]. The linearity of the relationship between continuous variables and the log odds of the outcome was verified using fractional polynomial. In presence of non-linearity assumption on a covariable, the fractional polynomial was retained.

We conducted two supplementary analyses. Models were run (i) using the cut-off for hippocampus and global WMH volumes calculated in the subsample of subjects with PSG data, and (ii) excluding APOE ε4 from the adjustment to better understand how this factor may influence the associations. Additionally, interactions between PSG data and follow-up time between MRI and PSG measurements (< 9.8 and ≥ 9.8 years, 9.8 years being the median between the two examinations) on the associations with hippocampal and global WMH volumes were tested to investigate whether time gap impacts the results, using the Wald Test. All analyses were performed using SAS version 9.4 and R version 4.1.0.

Results

Study population

After exclusion of subjects with dementia, history of stroke, and missing data on covariates, the study sample included 678 participants (Fig. 1). The participants' median age at baseline was 70.7 years (Q1-Q3 = 67.8–74.0) and 52.4% were women (Table 1).

MRI characteristics and self-reported sleep data are presented in Table 1. The median hippocampus volume was 5.8 cm^3 (Q1-Q3 = 5.2–6.2) and 0.7 cm^3 (Q1-Q3 = 0.3–2.7) for global WMH volume. Concerning sleep characteristics, 31.4% and 10.8% reported a short (≤ 6 h) and a long (≥ 9 h) nighttime sleep duration, respectively. More than half of the sample did not take a nap, 50.6% had good sleep efficiency, and 24.6% were dissatisfied with their sleep quality. EDS was reported by 9.1% of the participants, and 38.8% and 31.2% reported 1 and 2–3 insomnia symptoms, respectively. About 16% of the sample took sleeping pills at baseline with 11.7% using BZD, 4.3% BZD-like compounds, 1.2% antihistaminic compounds, 1.2% sedative antidepressants and 0.7% other medications.

In the subsample of the 176 participants with PSG assessment, the median age at baseline was 69.2 years (Q1-Q3 = 67.5–72.2), and 55.1% were women. The median hippocampus and global WMH volumes were 6.0 cm^3 (Q1-Q3 = 5.5–6.4) and 0.5 cm^3 (Q1-Q3 = 0.2–1.8), respectively. On the PSG, the median nighttime sleep duration was 6.1 h (Q1-Q3 = 5.4–6.9), sleep efficiency 67.9% (Q1-Q3 = 60.6–75.6), AHI 4.0/hour (Q1-Q3 = 1.3–11.8), O2 desaturation index 7.0 (Q1-Q3 = 3.0–15.0) and

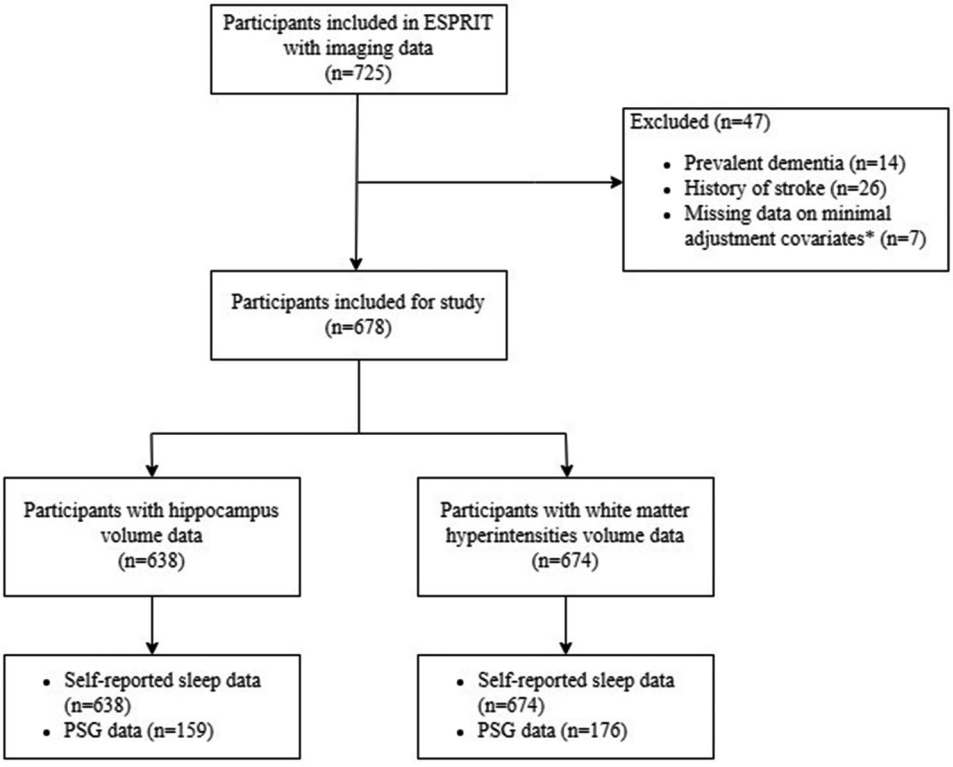

Fig. 1 Flow chart.* sex, age, educational level, and presence of APOE ε4

iPLMS 23.3/hour (Q1-Q3 = 9.8–43.1) (Table 1). Demographic, clinical, MRI, and self-reported sleep characteristics between participants with and without PSG data were compared in Supplementary Table 1. Participants with PSG data were younger than those without. They also had a higher level of education, consumed less alcohol, and exhibited better cardiovascular health scores. Additionally, these participants had larger hippocampal volumes, lower global WMH volumes, and took fewer naps. No significant differences were observed in other self-reported sleep characteristics between the two groups.

Associations between self-reported sleep, hippocampus, and global WMH volumes

Participants with low hippocampus volume were more likely to be women, older, users of sleeping pills, and had more frequently history of cardiovascular diseases and depressive status compared to participants with mild or large hippocampus volume (Table 2). After FDR correction, both early and late rising times were associated with a higher risk of having a low hippocampus volume. These associations remained significant even after further adjustment for behavioral and vascular risk factors variables (Table 3, Model 2), depressive status (Table 3, Model 4) or sleeping pills.

Participants with large global WMH volume were more often older, with history of cardiovascular diseases, and a worse cardiovascular health compared to those with low or mild global WMH volume (Table 2). An early rising time and a higher number of insomnia symptoms were associated with large global WMH volume, even after further adjustments and FDR correction (Table 4). Difficulty in initiating sleep was associated with large global WMH volume across all models (OR = 2.05, 95% CI = 1.38;3.05, Model 4) but not difficulty maintaining sleep (OR = 0.97, 95% CI = 0.68;1.38, Model 4) nor early morning awakenings (OR = 1.34, 95% CI = 0.87;2.06, Model 4) (Supplementary Table 2). A late bedtime was negatively associated with a large global WMH volume, regardless of adjustments and FDR correction (Table 4).

Associations between PSG data and hippocampus and global WMH volumes

No associations between polysomnographic parameters and hippocampus volume were found (Table 5). Higher percentage in REM sleep duration was associated with low global WMH volume, with similar trends for long sleep bouts duration, and N3 and REM sleep durations ($p = 0.05$ to 0.07, Table 6). In contrast, higher percentage of N2 sleep duration, longer duration of NREM sleep bouts, and higher index of PLMS were associated with large global WMH volume (Table 6). However, no associations remained significant after FDR correction. No interactions with time gap between MRI and PSG measurements were observed.

Table 1 Demographic, clinical, magnetic resonance imaging and self-reported and objective sleep characteristics

Variables	*n* (%) or median (Q1-Q3)
Demographic and clinical characteristics (*n* = 678)	
Sex	
Men	323 (47.64)
Women	355 (52.36)
Age (years)	70.7 (67.8–74.0)
Educational level	
≥ Primary	501 (73.89)
< Primary	177 (26.11)
APOE ε4 carrier	
< 1 allele	539 (79.50)
≥ 1 allele	139 (20.50)
Alcohol (g/day)	
< 12	395 (59.58)
[12;36[	189 (28.51)
≥ 36	79 (11.92)
History of cardiovascular diseases	
No	558 (82.42)
Yes	119 (17.58)
Cardiovascular health score	8.0 (7.0–10.0)
Depressive status [a]	
No	484 (71.81)
Yes	190 (28.19)
Sleeping pills [b]	
No	571 (84.22)
Yes	107 (15.78)
MRI characteristics (*n* = 678)	
Intracranial volume (cm^3)	1190.2 (1115.9-1273.6)
Hippocampus volume (cm^3)	5.8 (5.2–6.2)
Hippocampus volume (cm^3)	
≥ 5.4 (2nd and 3rd tertiles)	435 (68.2)
< 5.4 (1st tertile)	203 (31.8)
White matter hyperintensities volume (cm^3)	0.70 (0.30–2.70)
White matter hyperintensities volume (cm^3)	
≤ 1.6 (1st and 2nd tertiles)	455 (67.51)
> 1.6 (3rd tertile)	219 (32.49)
Self-reported sleep characteristics (*n* = 678)	
Nighttime sleep duration (h)	
≤ 6	201 (31.41)
]6;9[	370 (57.81)
≥ 9	69 (10.78)
Napping	
No	355 (53.79)
Infrequent/short	108 (16.36)
Regular long	197 (29.85)
Sleep efficiency	
Good (≥ 85%)	315 (49.45)
Poor (< 85%)	322 (50.55)
Bedtime	
≤ 9 pm	37 (5.48)
]9–11[pm	255 (37.78)
≥ 11 pm	383 (56.74)
Rising time	
≤ 6 am	78 (11.56)

Table 1 (continued)

Variables	*n* (%) or median (Q1-Q3)
Demographic and clinical characteristics (*n* = 678)	
]6–8] am	492 (72.89)
> 8 am	105 (15.56)
Excessive daytime sleepiness	
No	600 (90.91)
Yes	60 (9.09)
Satisfaction in sleep quality	
Yes	500 (75.41)
No	163 (24.59)
Number of insomnia symptoms	
0	196 (29.97)
1	254 (38.84)
2–3	204 (31.19)
Objective (via polysomnography) characteristics (*n* = 176)	
Nighttime sleep duration (h)	6.1 (5.4–6.9)
N1 sleep duration (min)	22.5 (14.8–30.0)
% N1 sleep duration	6.0 (4.1–8.4)
N2 sleep duration (min)	227.8 (194.3-260.3)
% N2 sleep duration	61.9 (57.9–68.1)
N3 sleep duration (min)	39.8 (25.3–58.0)
% N3 sleep duration	11.4 (7.3–15.9)
REM sleep duration (min)	71.0 (54.8–85.0)
% REM sleep duration	19.3 (15.6–22.8)
SB duration (min)	27.3 (17.8–40.8)
SB NREM duration (min)	4.0 (2.5–7.3)
SB REM duration (min)	0.0 (0.0–4.0)
Sleep efficiency (%)	67.9 (60.6–75.6)
Sleep latency (min)	86.5 (64.5-134.8)
WASO (min)	173.8 (130.5-218.8)
AHI (/h)	4.0 (1.3–11.8)
iPLMS	23.3 (9.8–43.1)
O2 desaturation index > 3%	7.0 (3.0–15.0)

Abbreviations AHI, apnea-hypopnea index; iPLMS, index of periodic leg movements during sleep; N1, stage 1; N2, stage 2; N3, stage 3; NREM, non-rapid eye movement; REM, rapid eye movement; SB, sleep bout; WASO, wake after sleep onset

[a] Center for Epidemiological Studies-Depression Scale ≥ 16 or current antidepressant treatment

[b] including benzodiazepine, benzodiazepine like compounds and miscellaneous medications

Supplementary analyses

When using the MRI data cut-off of the subsample with PSG data, no association was observed between PSG characteristics and hippocampus volume (Supplementary Table 3), aligning with the main results. Across all models, longer N3 sleep duration was associated with a low global WMH volume, whereas higher percentage of N2 sleep duration and higher iPLMS were associated with a large global WMH volume (Supplementary Table 4). However, the results did not remain after FDR correction, as observed in the main results. Removing adjustment for APOE ε4 did not substantially change the results (Supplementary Tables 5–8).

Discussion

In a sample of community-dwelling older adults without dementia, volumes of hippocampus and global WMH had distinct associations with clinical sleep and PSG characteristics. The strongest findings were the association between early or late rising times and lower hippocampal volume. Self-reported early rising time and insomnia symptoms were associated with larger global WMH volume, while late bedtime was associated with lower global WMH volume. These results persisted even after adjusting for demographic characteristics, intracranial volume, APOE ε4 status, cardiovascular health, depressive status and sleeping pills use.

To the best of our knowledge, few studies have investigated the relationship between sleep timing and hippocampal volume [50]. A cross-sectional study on 90

Table 2 Baseline demographic and clinical characteristics of participants according to the volume of hippocampus and global white matter hyperintensities

	Hippocampus volume (cm^3)						**White matter hyperintensities volume (cm^3)**					
	≥ 5.4 *n* = 435		**< 5.4 *n* = 203**				**≤ 1.6 *n* = 455**		**> 1.6 *n* = 219**			
Variables	n	%	n	%	OR [95% CI]*	Overall p	n	%	n	%	OR [95% CI]*	Overall p
Sex						< 0.0001						0.58
Men	237	54.48	64	31.53	1		214	47.03	108	49.32	1	
Women	198	45.52	139	68.47	2.60 [1.83;3.69]		241	52.97	111	50.68	0.91 [0.66;1.26]	
Age (years)[a]	70.9	(± 4.0)	72.0	(± 4.0)	1.07 [1.02;1.11]	0.002	70.9	(± 3.9)	72.0	(± 4.1)	1.07 [1.03;1.11]	0.0009
Educational level						0.28						0.87
≥ Primary	326	74.94	144	70.94	1		336	73.85	163	74.43	1	
< Primary	109	25.06	59	29.06	1.23 [0.84;1.78]		119	26.15	56	25.57	0.97 [0.67;1.40]	
APOE ε4 carrier						0.40						0.07
< 1 allele	349	80.23	157	77.34	1		370	81.32	165	75.34	1	
≥ 1 allele	86	19.77	46	22.66	1.19 [0.79;1.78]		85	18.68	54	24.66	1.42 [0.97;2.10]	
Alcohol (g/day)						0.37						0.43
< 12	251	58.24	123	63.40	1		274	61.16	119	56.40	1	
[12;36[	126	29.23	53	27.32	0.86 [0.58;1.26]		121	27.01	67	31.75	1.27 [0.88;1.84]	
≥ 36	54	12.53	18	9.28	0.68 [0.38;1.21]		53	11.83	25	11.85	1.09 [0.64;1.83]	
History of cardiovascular diseases						0.02						0.05
No	371	85.48	158	77.83	1		385	84.62	171	78.44	1	
Yes	63	14.52	45	22.17	1.68 [1.10;2.57]		70	15.38	47	21.56	1.51 [1.00;2.28]	
Cardiovascular health score [a]	8.3	(± 1.9)	8.3	(± 2.0)	0.99 [0.91;1.08]	0.78	8.5	(± 1.9)	7.9	(± 1.8)	0.86 [0.79;0.94]	0.0007
Depressive status[b]						0.003						0.60
No	327	75.52	129	64.18	1		328	72.57	154	70.64	1	
Yes	106	24.48	72	35.82	1.72 [1.20;2.47]		124	27.43	64	29.36	1.10 [0.77;1.57]	
Sleeping pills[c]						0.01						0.90
No	377	86.67	160	78.82	1		384	84.40	184	84.02	1	
Yes	58	13.33	43	21.18	1.75 [1.13;2.70]		71	15.60	35	15.98	1.03 [0.66;1.60]	

Abbreviations APOE ε4, apolipoprotein E gene ε4 allele; CI, confidence interval; OR, odds ratio

* Crude models

[a] continuous variable is expressed as mean (± standard-deviation)

[b] Center for Epidemiological Studies-Depression Scale ≥ 16 or current antidepressant treatment

[c] including benzodiazepine, benzodiazepine like compounds and miscellaneous medications

healthy university students found a relationship between a small hippocampal volume and self-reported late bedtime (≥ 1 am), with a similar trend for late rising time (≥ 10 am) [50]. Our findings align with this prior study, demonstrating an association between early and late self-reported rising times and a low hippocampal volume. Although our results for bedtime did not reach significance, a trend was reported between both early and late bedtimes and hippocampal volumes. One potential explanation for these associations may be that altered sleep timing reflect disrupted circadian rhythms, potentially accelerating hippocampal atrophy through impacts on cerebral blood flow, amyloid clearance, glymphatic metabolism, or inflammation processes [51]. Altered sleep timing is also often related with short sleep duration, medical conditions such as depression, and medication use. However, in our study, neither self-reported nor objective sleep durations were associated with hippocampal volume, and the results remained consistent after adjustment for depressive status or sleeping pills. Also, we observed no association between PSG data and hippocampal volume. Our results are consistent with a study involving 492 participants that reported no link between slow-wave sleep and REM sleep durations and hippocampal volume [18]. In contrast, two other studies highlighted (i) a relationship between SDB and hippocampal atrophy in cognitively unimpaired but amyloid-positive older adults [12]; and (ii) an association between higher iPLMS and lower hippocampal volume in middle-aged individuals [13]. These discrepancies may be due to differences in study populations, different severity of AHI (very low in our sample) and iPLMS (fairly important in our sample), and sample sizes. Additionally, there was a significant time gap between PSG and MRI scans in our study, and MRI was performed before PSG assessments. This temporal discrepancy may complicate data interpretation and potentially mask any relationship between PSG data and hippocampal volume.

Table 3 Association between self-reported sleep parameters and hippocampus volume ($n=638$)

	Hippocampus volume (cm^3)											
	≥ 5.4 $n=435$		< 5.4 $n=203$		Model 1		Model 2		Model 3		Model 4	
Variables	**n**	**%**	**n**	**%**	**OR [95% CI]**	**Overall p**	**OR [95% CI]**	**Overall p**	**OR [95% CI]**	**Overall p**	**OR [95% CI]**	**Overall p**
Nighttime sleep duration (h)						0.23		0.20		0.21		0.21
≤ 6	119	29.10	74	38.34	1.33 [0.90;1.98]		1.36 [0.91;2.03]		1.33 [0.89;2.00]		1.35 [0.90;2.01]	
]6;9[	246	60.15	95	49.22	1		1		1		1	
≥ 9	44	10.76	24	12.44	1.47 [0.83;2.60]		1.48 [0.83;2.63]		1.51 [0.85;2.69]		1.49 [0.84;2.65]	
Napping						0.25		0.16		0.16		0.15
No	213	50.35	122	61.93	1		1		1		1	
Infrequent/short	72	17.02	27	13.71	0.87 [0.51;1.46]		0.83 [0.49;1.40]		0.79 [0.47;1.35]		0.81 [0.48;1.38]	
Regular long	138	32.62	48	24.37	0.70 [0.46;1.07]		0.66 [0.43;1.01]		0.67 [0.43;1.02]		0.66 [0.43;1.00]	
Sleep efficiency						0.53		0.48		0.55		0.51
Good (≥ 85%)	206	50.74	85	44.04	1		1		1		1	
Poor (< 85%)	200	49.26	108	55.96	1.12 [0.78;1.62]		1.14 [0.79;1.65]		1.12 [0.77;1.62]		1.13 [0.78;1.64]	
Bedtime						0.78		0.85		0.85		0.82
≤ 9 pm	22	5.09	12	5.91	1.29 [0.58;2.84]		1.19 [0.53;2.67]		1.19 [0.53;2.67]		1.19 [0.53;2.67]	
]9–11[pm	166	38.43	76	37.44	1		1		1		1	
≥ 11 pm	244	56.48	115	56.65	1.10 [0.76;1.58]		1.10 [0.76;1.58]		1.09 [0.75;1.59]		1.11 [0.77;1.61]	
Rising time						0.0005*		0.0009*		0.0005*		0.001*
≤ 6 am	40	9.26	29	14.29	2.09 [1.21;3.63]		2.03 [1.17;3.53]		2.04 [1.16;3.56]		2.03 [1.17;3.53]	
]6–8] am	336	77.78	131	64.53	1		1		1		1	
> 8 am	56	12.96	43	21.18	2.21 [1.38;3.53]		2.16 [1.34;3.47]		2.29 [1.42;3.69]		2.14 [1.33;3.43]	
Excessive daytime sleepiness, yes	44	10.40	12	6.06	0.78 [0.39;1.55]	0.48	0.76 [0.38;1.50]	0.43	0.75 [0.37;1.49]	0.41	0.76 [0.38;1.51]	0.43
Satisfaction in sleep quality, no	95	22.20	58	29.74	1.26 [0.84;1.88]	0.27	1.29 [0.85;1.94]	0.23	1.23 [0.81;1.86]	0.34	1.25 [0.82;1.89]	0.30
Number of insomnia symptoms						0.79		0.72		0.94		0.81
0	133	31.82	51	26.02	1		1		1		1	
1	162	38.76	73	37.24	1.00 [0.64;1.57]		1.00 [0.63;1.57]		0.99 [0.63;1.57]		1.00 [0.63;1.57]	
2–3	123	29.43	72	36.73	1.15 [0.72;1.83]		1.17 [0.73;1.88]		1.07 [0.66;1.75]		1.14 [0.70;1.84]	

Abbreviations CI, confidence interval; OR, odds ratio

Model 1 was adjusted for age, sex, educational level, APOE ε4 carrier, and intracranial volume

Model 2 was adjusted for all the covariates in model 1 plus cardiovascular health and history of cardiovascular diseases

Model 3 was adjusted for all the covariates in model 2 plus depressive status

Model 4 was adjusted for all the covariates in model 2 plus sleeping pills

* Indicates remaining significant even after FDR correction

We found an association between early rising time and larger WMH burden, which aligns with a previous study indicating a positive association between waking-up before 5 am and presence of periventricular white matter lesions in older adults [52]. Unlike previous research [25, 52], we observed a relationship between insomnia symptoms, especially difficulty initiating sleep, and WMH burden in a dose-response pattern. This is consistent

Table 4 Association between self-reported sleep parameters and global white matter hyperintensities volume ($n=674$)

White matter hyperintensities volume (cm^3)												
	≤ 1.6 $n=455$		> 1.6 $n=219$		Model 1		Model 2		Model 3		Model 4	
Variables	**n**	**%**	**n**	**%**	**OR [95% CI]**	**Overall p**	**OR [95% CI]**	**Overall p**	**OR [95% CI]**	**Overall p**	**OR [95% CI]**	**Overall p**
Nighttime sleep duration (h)						0.25		0.21		0.21		0.20
≤ 6	129	30.14	72	34.45	1.22 [0.83;1.79]		1.23 [0.83;1.81]		1.22 [0.82;1.82]		1.23 [0.84;1.83]	
]6;9[	247	57.71	120	57.42	1		1		1		1	
≥ 9	52	12.15	17	8.13	0.71 [0.38;1.31]		0.69 [0.37;1.28]		0.68 [0.36;1.26]		0.69 [0.37;1.27]	
Napping						0.47		0.43		0.47		0.44
No	240	54.05	115	54.25	1		1		1		1	
Infrequent/short	79	17.79	28	13.21	0.75 [0.45;1.24]		0.72 [0.43;1.20]		0.73 [0.43;1.22]		0.72 [0.43;1.20]	
Regular long	125	28.15	69	32.55	1.03 [0.70;1.52]		0.97 [0.66;1.44]		0.97 [0.65;1.44]		0.98 [0.66;1.45]	
Sleep efficiency						0.88		0.80		0.79		0.78
Good (≥ 85%)	211	49.65	102	48.80	1		1		1		1	
Poor (< 85%)	214	50.35	107	51.20	1.03 [0.73;1.46]		1.05 [0.74;1.49]		1.05 [0.74;1.50]		1.05 [0.74;1.50]	
Bedtime						0.004*		0.002*		0.002*		0.002*
≤ 9 pm	19	4.20	17	7.76	1.41 [0.68;2.90]		1.27 [0.61;2.66]		1.24 [0.59;2.61]		1.27 [0.61;2.64]	
]9–11[pm	155	34.29	98	44.75	1		1		1		1	
≥ 11 pm	278	61.50	104	47.49	0.60 [0.42;0.85]		0.57 [0.40;0.81]		0.56 [0.39;0.80]		0.56 [0.39;0.80]	
Rising time						0.004*		0.003*		0.001*		0.003*
≤ 6 am	39	8.61	39	17.89	2.10 [1.27;3.46]		2.06 [1.24;3.43]		2.16 [1.29;3.61]		2.06 [1.24;3.43]	
]6–8] am	336	74.17	153	70.18	1		1		1		1	
> 8 am	78	17.22	26	11.93	0.75 [0.45;1.23]		0.69 [0.42;1.15]		0.64 [0.38;1.08]		0.69 [0.42;1.15]	
Excessive daytime sleepiness, yes	36	8.13	23	10.80	1.62 [0.90;2.90]	0.10	1.57 [0.87;2.83]	0.13	1.56 [0.86;2.81]	0.14	1.57 [0.87;2.83]	0.13
Satisfaction in sleep quality, no	108	24.22	55	25.82	1.13 [0.76;1.67]	0.55	1.13 [0.76;1.69]	0.54	1.18 [0.78;1.78]	0.42	1.14 [0.76;1.71]	0.53
Number of insomnia symptoms						0.02		0.01*		0.01*		0.01*
0	146	33.26	48	22.75	1		1		1		1	
1	164	37.36	89	42.18	1.74 [1.13;2.69]		1.84 [1.18;2.86]		1.85 [1.19;2.88]		1.84 [1.18;2.86]	
2–3	129	29.38	74	35.07	1.81 [1.14;2.89]		1.88 [1.17;3.03]		1.96 [1.20;3.18]		1.91 [1.18;3.09]	

Abbreviations CI, confidence interval; OR, odds ratio

Model 1 was adjusted for age, sex, educational level, APOE ε4 carrier, and intracranial volume

Model 2 was adjusted for all the covariates in model 1 plus cardiovascular health and history of cardiovascular diseases

Model 3 was adjusted for all the covariates in model 2 plus depressive status

Model 4 was adjusted for all the covariates in model 2 plus sleeping pills

* Indicates remaining significant even after FDR correction

with our findings of an association between late bedtime and lower global WMH volumes, with insomnia risk generally decreasing with reduced time in bed [53]. This association might also be due to lifestyle factors associated with a late bedtime (e.g., higher cognitive or social engagement during evening hours) which could mitigate some of the potential negative health impacts typically linked to later chronotypes. Further studies are needed to replicate this finding. Overall, early rising time and insomnia symptoms might be clinical sleep markers

Table 5 Association between polysomnography sleep parameters and hippocampus volume ($n = 159$)

	Hippocampus volume (cm^3)											
	≥ 5.4 $n = 124$		< 5.4 $n = 35$		Model 1		Model 2		Model 3		Model 4	
Variables	**median**	**(Q1-Q3)**	**median**	**(Q1-Q3)**	**OR [95% CI]**	**Overall p**	**OR [95% CI]**	**Overall p**	**OR [95% CI]**	**Overall p**	**OR [95% CI]**	**Overall p**
Nighttime sleep duration (h)	6.0	(5.3–6.9)	6.3	(5.8–7.1)	1.21 [0.84;1.74]	0.30	1.25 [0.87;1.80]	0.23	1.32 [0.89;1.95]	0.24	1.26 [0.87;1.83]	0.22
N1 sleep duration (min) [a]	23.3	(15.0-32.5)	22.0	(14.5–26.5)	0.89 [0.54;1.46]	0.64	0.86 [0.52;1.42]	0.56	0.86 [0.52;1.43]	0.56	0.86 [0.52;1.41]	0.55
% N1 sleep duration [b]	6.3	(4.1–9.3)	5.6	(4.3–7.3)	0.76 [0.41;1.43]	0.40	0.72 [0.39;1.35]	0.31	0.70 [0.37;1.35]	0.29	0.72 [0.38;1.34]	0.29
N2 sleep duration (min) [c]	223.3	(186.3–253.0)	235.0	(203.0-271.5)	1.23 [0.81;1.88]	0.34	1.21 [0.79;1.85]	0.38	1.23 [0.79;1.92]	0.36	1.23 [0.80;1.89]	0.35
% N2 sleep duration [d]	61.3	(55.3–66.5)	61.9	(58.8–68.7)	1.11 [0.71;1.74]	0.63	1.03 [0.65;1.63]	0.90	0.98 [0.60;1.58]	0.92	1.04 [0.66;1.66]	0.85
N3 sleep duration (min) [e]	38.5	(25.0–58.0)	46.0	(27.5–66.5)	1.17 [0.78;1.76]	0.44	1.30 [0.85;1.99]	0.22	1.36 [0.88;2.09]	0.17	1.29 [0.84;1.98]	0.24
% N3 sleep duration [b]	10.8	(7.4–16.1)	12.4	(7.1–16.7)	1.01 [0.75;1.37]	0.92	1.08 [0.80;1.47]	0.61	1.10 [0.80;1.51]	0.56	1.07 [0.78;1.46]	0.68
REM sleep duration (min) [e]	72.8	(57.3–89.0)	70.0	(51.0-81.5)	1.02 [0.68;1.54]	0.92	1.08 [0.71;1.64]	0.71	1.17 [0.75;1.83]	0.49	1.10 [0.72;1.68]	0.66
% REM sleep duration [b]	20.0	(16.0-23.2)	18.4	(13.3–21.4)	0.94 [0.67;1.33]	0.73	0.97 [0.69;1.38]	0.88	1.02 [0.70;1.49]	0.90	0.98 [0.69;1.40]	0.91
SB duration (min) [g]	27.5	(16.8–40.8)	25.8	(18.0-40.5)	0.72 [0.45;1.17]	0.19	0.78 [0.47;1.27]	0.32	0.77 [0.47;1.28]	0.32	0.78 [0.47;1.28]	0.32
NREM SB duration (min) [b]	3.8	(2.5–7.4)	5.0	(3.0–7.0)	0.85 [0.53;1.39]	0.52	0.80 [0.50;1.30]	0.38	0.84 [0.51;1.39]	0.49	0.79 [0.49;1.29]	0.35
REM SB duration (min) [b]	0.5	(0.0–4.0)	0.0	(0.0-4.5)	0.92 [0.65;1.29]	0.62	0.95 [0.68;1.34]	0.79	0.95 [0.66;1.36]	0.77	0.96 [0.68;1.35]	0.81
Sleep efficiency (%) [d]	66.7	(59.5–75.5)	70.2	(63.8–78.6)	1.39 [0.93;2.08]	0.11	1.38 [0.92;2.06]	0.12	1.42 [0.93;2.16]	0.10	1.43 [0.94;2.18]	0.10
Sleep latency (min) [c]	86.5	(64.0-133.8)	84.5	(68.0-143.5)	1.17 [0.76;1.79]	0.47	1.21 [0.77;1.88]	0.41	1.32 [0.85;2.07]	0.22	1.21 [0.78;1.89]	0.40
WASO (min) [c]	180.3	(130.5-226.8)	158.5	(121.0-202.5)	0.70 [0.47;1.06]	0.09	0.71 [0.47;1.07]	0.10	0.69 [0.45;1.05]	0.08	0.68 [0.44;1.05]	0.08
AHI (/h) [d]	4.3	(1.6–11.9)	4.0	(0.2–10.5)	1.01 [0.66;1.53]	0.98	0.97 [0.64;1.46]	0.87	1.04 [0.69;1.58]	0.84	0.96 [0.63;1.45]	0.84
iPLMS [e]	23.3	(10.4–37.6)	15.7	(6.8–46.0)	1.12 [0.69;1.83]	0.65	1.21 [0.73;2.00]	0.46	1.09 [0.65;1.82]	0.74	1.19 [0.72;1.98]	0.49
O2 desaturation index > 3% [d]	7.0	(4.0–15.0)	8.0	(4.0–14.0)	0.95 [0.60;1.52]	0.84	1.02 [0.62;1.68]	0.94	1.13 [0.69;1.84]	0.63	1.01 [0.61;1.68]	0.96

Abbreviations AHI, apnea-hypopnea index; CI, confidence interval; iPLMS, index of periodic limb movements of sleep; N1, stage 1; N2, stage 2; N3, stage 3; NREM, non-rapid eye movement; OR, odds ratio; REM, rapid eye movement; SB, sleep bout; WASO, wake after sleep onset

Model 1 was adjusted for age, sex, educational level, APOE ε4 carrier, and intracranial volume

Model 2 was adjusted for all the covariates in model 1 plus cardiovascular health and history of cardiovascular diseases

Model 3 was adjusted for all the covariates in model 2 plus depressive status

Model 4 was adjusted for all the covariates in model 2 plus sleeping pills

* Indicates remaining significant even after FDR correction

[a] OR for 15 units increase; [b] OR for 5 min increase; [c] OR for 60 min increase; [d] OR for 10 min increase; [e] OR for 25 units increase; [f] OR for 10 units increase; [g] OR for 20 units increase

Table 6 Association between polysomnography sleep parameters and global white matter hyperintensities volume ($n = 176$)

	White matter hyperintensities volume											
	≤ 1.6 $n = 131$		**> 1.6** $n = 45$		Model 1		Model 2		Model 3		Model 4	
Variables	median	(Q1-Q3)	median	(Q1-Q3)	OR [95% CI]	Overall p	OR [95% CI]	Overall p	OR [95% CI]	Overall p	OR [95% CI]	Overall p
Nighttime sleep duration (h)	6.1	(5.4–6.9)	6.0	(5.5-7.0)	0.97 [0.70;1.32]	0.83	0.98 [0.71;1.34]	0.89	0.98 [0.71;1.35]	0.92	0.99 [0.72;1.36]	0.93
N1 sleep duration (min) [a]	22.5	(15.0-30.5)	22.0	(11.5–29.5)	1.07 [0.74;1.56]	0.72	1.06 [0.73;1.55]	0.76	1.06 [0.73;1.55]	0.75	1.05 [0.72;1.54]	0.79
% N1 sleep duration [b]	6.0	(4.3–8.4)	6.1	(3.6–9.3)	1.12 [0.72;1.73]	0.61	1.10 [0.70;1.71]	0.68	1.11 [0.71;1.72]	0.70	1.09 [0.70;1.69]	0.72
N2 sleep duration (min) [c]	224.5	(186.5-257.5)	234.5	(210.5-268.5)	1.32 [0.90;1.94]	0.15	1.30 [0.89;1.91]	0.18	1.30 [0.88;1.91]	0.18	1.34 [0.90;1.98]	0.15
% N2 sleep duration [d]	60.8	(55.4–66.6)	65.5	(61.7–69.7)	1.69 [1.11;2.57]	**0.02**	1.63 [1.06;2.51]	**0.03**	1.60 [1.04;2.46]	**0.03**	1.69 [1.09;2.62]	**0.02**
N3 sleep duration (min) [e]	42.0	(27.5–61.5)	31.0	(21.0-45.5)	0.70 [0.48;1.04]	0.07	0.73 [0.49;1.08]	0.11	0.73 [0.50;1.08]	0.12	0.69 [0.46;1.04]	0.07
% N3 sleep duration [b]	12.0	(7.7–16.9)	9.9	(5.4–13.6)	0.81 [0.61;1.07]	0.14	0.83 [0.62;1.11]	0.20	0.83 [0.62;1.11]	0.21	0.79 [0.58;1.07]	0.13
REM sleep duration (min) [e]	72.5	(57.0–89.0)	67.0	(46.0-81.5)	0.67 [0.46;0.96]	**0.03**	0.68 [0.47;0.99]	0.05	0.69 [0.47;1.00]	0.05	0.69 [0.48;1.01]	0.05
% REM sleep duration [b]	19.8	(16.0-23.1)	17.1	(13.3–20.6)	0.68 [0.49;0.93]	**0.02**	0.69 [0.50;0.95]	**0.02**	0.69 [0.50;0.96]	**0.03**	0.70 [0.50;0.96]	**0.03**
SB duration (min) [g]	30.1	(18.8–42.5)	22.5	(14.5–36.0)	0.63 [0.40;0.99]	**0.04**	0.64 [0.40;1.01]	0.05	0.64 [0.40;1.01]	0.05	0.64 [0.40;1.01]	0.05
NREM SB duration (min) [b]	4.0	(2.5-7.0)	4.0	(3.0-9.5)	1.48 [1.04;2.10]	**0.03**	1.45 [1.01;2.06]	**0.04**	1.45 [1.01;2.06]	**0.04**	1.46 [1.02;2.09]	**0.04**
REM SB duration (min) [b]	0.0	(0.0-4.5)	0.5	(0.0-2.5)	0.84 [0.60;1.16]	0.29	0.85 [0.61;1.19]	0.36	0.85 [0.61;1.20]	0.36	0.86 [0.61;1.20]	0.37
Sleep efficiency (%) [d]	67.7	(59.9–74.9)	69.6	(61.4–76.4)	1.05 [0.76;1.47]	0.76	1.06 [0.76;1.48]	0.73	1.05 [0.75;1.47]	0.78	1.09 [0.77;1.53]	0.64
Sleep latency (min) [c]	87.0	(66.0-143.5)	84.0	(60.5-118.5)	0.86 [0.58;1.26]	0.44	0.89 [0.60;1.32]	0.55	0.90 [0.61;1.33]	0.59	0.89 [0.60;1.33]	0.57
WASO (min) [c]	174.5	(132.0-226.0)	164.5	(129.0-203.0)	0.88 [0.63;1.24]	0.47	0.88 [0.63;1.23]	0.46	0.89 [0.63;1.25]	0.50	0.85 [0.60;1.21]	0.37
AHI (/h) [d]	3.9	(1.1–11.8)	4.0	(1.6–11.9)	1.01 [0.74;1.39]	0.93	0.98 [0.71;1.35]	0.91	1.00 [0.73;1.37]	0.99	0.97 [0.70;1.34]	0.85
iPLMS [e]	22.1	(8.4–34.3)	29.1	(10.5–50.9)	1.44 [0.98;2.13]	0.06	1.53 [1.03;2.27]	**0.04**	1.50 [1.01;2.24]	**0.046**	1.52 [1.02;2.26]	**0.04**
O2 desaturation index > 3% [d]	6.5	(3.0–17.0)	7.0	(4.0–12.0)	0.92 [0.63;1.34]	0.66	0.90 [0.61;1.33]	0.59	0.91 [0.62;1.34]	0.63	0.89 [0.60;1.32]	0.57

Abbreviations AHI, apnea-hypopnea index; CI, confidence interval; iPLMS, index of periodic limb movements of sleep; N1, stage 1; N2, stage 2; N3, stage 3; NREM, non-rapid eye movement; OR, odds ratio; REM, rapid eye movement; SB, sleep bout; WASO, wake after sleep onset

Model 1 was adjusted for age, sex, educational level, APOE ε4 carrier, and intracranial volume

Model 2 was adjusted for all the covariates in model 1 plus cardiovascular health and history of cardiovascular diseases

Model 3 was adjusted for all the covariates in model 2 plus depressive status

Model 4 was adjusted for all the covariates in model 2 plus sleeping pills

* Indicates remaining significant even after FDR correction

[a] OR for 15 units increase; [b] OR for 5 min increase; [c] OR for 60 min increase; [d] OR for 10 min increase; [e] OR for 25 units increase; [f] OR for 10 units increase; [g] OR for 20 units increase

of brain structure in older adults. However, we cannot rule out that these clinical sleep parameters were better explained by underlying associated pathologies, and that the presence of WMH may conversely cause sleep problems. We also showed that global WMH volume trends were larger with higher percentage of N2 sleep duration, longer duration of NREM sleep bouts (i.e., that often include N2 sleep) while they were lower when participants had longer sleep bout durations and REM and N3 sleep. Although some studies have highlighted an

association between short REM sleep duration and cognitive impairment [54, 55], we did not observe an association between REM sleep and hippocampal volume. However, we observed an association between higher percentage of REM sleep duration and low global WHM volume. Further studies are needed to replicate these results and to better understand the underlying mechanisms. In contrast to previous studies [25, 27, 56], we found no association between self-reported or objective total sleep durations and WMH burden. Several hypotheses may explain the mechanisms through which sleep might impact WMH. Fragmented sleep may impair the glymphatic clearance system in the brain, leading to an increase in the concentration of β-amyloid which can alter white matter integrity [57]. Altered sleep may also impact myelination and neuronal membrane maintenance by causing stress, and by increasing the risk of several vascular and metabolic risk factors such as hypertension and inflammatory markers [58, 59]. Previous literature also suggested a strong association between OSA and WMH volume [24], but we found no association with AHI, potentially due to low recruitment of participants with SDB. Moreover, an underestimation of the effects could be linked to better health of individuals with PSG, thus with better MRI results (Supplementary Table 1). In contrast, we highlighted a link between high iPLMS and large global WMH volume, similar to findings in a case-control study involving 60 participants [28], but not confirmed in two recent studies [13, 60]. This discrepancy may be due to methodological differences, study populations, and the different definition of white matter lesions.

Taken together, these results are consistent with the general view that sleep alteration can play a role in brain damage, thus at risk for Alzheimer's disease and vascular dementia. Sleep timing, early and late rising time, were related to hippocampal and global WMH volumes, whereas insomnia symptoms and parameters related to sleep continuity and fragmentation were only linked to WMH burden.

The strengths of the study include the use of a general community-based sample and the consideration of numerous predictors, while most previous studies have focused on only a few sleep parameters. We also accounted for numerous key confounders, including depressive status and use of sleeping pills. MRI scans were acquired in accordance with current clinical standards, providing quantitative measures with a high level of reliability. Additionally, we used both self-reported and objective sleep data, including PSG data, the gold-standard for sleep assessment. However, the results should be interpreted in light of some limitations. An important limitation lies in the cross-sectional design, as it lacks a longitudinal assessment of brain MRI to monitor hippocampal atrophy and increasing WMH burden. Moreover, the number of PSGs was limited and these were assessed subsequently to MRI data, leading to temporal discordance with respect to our hypothesis which might bias the associations. However, the time gap between MRI and PSG measurements did not seem to impact the results, as no interactions were observed. Due to the inherent limitations of a cross-sectional design, any causal conclusions regarding the direction of the association between sleep and MRI data cannot be made. Although many potential confounders were considered, we cannot exclude the possibility that other potential confounders, such as participants' chronotype, may impact the results. Furthermore, although we attempted to minimize multiple testing by correcting for multiple comparisons, this problem may have increased the risk of type 1 error. To enhance the generalizability and reliability of these findings, further studies should be conducted on larger and more diverse population samples. Most importantly, longitudinal studies with repeated MRI brain data are needed to clarify the role of sleep and its timing on brain damage (neurodegeneration and vascular pathways) and long-term cognitive outcomes.

In conclusion, our study revealed that participants who reported extreme rising times exhibited smaller hippocampal volumes, while those reporting early rising time and insomnia symptoms had larger global WMH volumes. Conversely, participants who reported a late bedtime showed lower global WMH volumes. These findings suggest a significant role for sleep timing and symptoms of insomnia in the dementia context, underscoring the importance of further research into the relationship between sleep, circadian rhythm, and brain structure to enhance our understanding of these links to dementia.

Abbreviations

AD/ADRD	Alzheimer's Disease and Related Dementias
AHI	Apnea-Hypopnea Index
APOE ε4	Apolipoprotein e-ε4
BMI	Body Mass Index
BZD	benzodiazepines
CES-D	Center for Epidemiological Studies-Depression
CI	Confidence Interval
EDS	Excessive Daytime Sleepiness
FDR	False Discovery Rate
iPLMS	Index of Periodic Limb Movements of Sleep
MRI	Magnetic Resonance Imaging
N1	Stage 1
N2	Stage 2
N3	Stage 3
NREM	Non-Rapid Eye Movement
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
PLM	Periodic Limb Movement
PSG	Polysomnography
REM	Rapid Eye Movement
ROI	Region Of Interest
SB	Sleep Bout
SDB	Sleep-Disordered Breathing
WASO	Wake After Sleep Onset
WMH	White Matter Hyperintensity

Supplementary Information

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Supplementary Material 1

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Author contributions
C.C. conceived and designed the study, analyzed the data, interpreted the study findings, and drafted the manuscript. S.A. and J.J.M. interpreted the study findings and critically revised the manuscript. I.J. and Y.D. conceived and designed the study, interpreted the study findings, and reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All participants signed informed consent, and the Ethics Committee of the Hospital of Kremlin-Bicêtre and Sud-Méditerranée III, Paris, France, approved the study protocol. The research was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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