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Received: 11 December 2025 | Revised: 19 February 2026 | Accepted: 11 March 2026

DOI: 10.1002/alz.71376

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Night-to-night rapid eye movement sleep variability: A relevant marker of early amyloid-β deposition

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Funding information
European Union's Horizon 2020 Research and Innovation Program; Institut National de la Santé et de la Recherche Médicale; Fondation d'entreprise MMA des Entrepreneurs du Futur; Région Normandie

Abstract

INTRODUCTION: Sleep disturbances are prevalent in patients with Alzheimer's disease (AD) and may emerge before overt clinical symptoms. We characterized sleep alterations in cognitively unimpaired older adults with cerebral amyloid deposition, and assessed their associations with regional amyloid deposition and cognitive and psychoaffective outcomes.

METHODS: Seventy-six older adults (69.1 ± 3.4 years, 63.2% female) underwent a multi-night (4.5 ± 0.8 nights) objective sleep assessment using the Somno-Art wearable device, Florbetapir-positron emission tomography (PET) scanning, and an extensive neuropsychological and psychoaffective evaluation.

RESULTS: Amyloid β (Aβ)-positive individuals had a shorter total sleep time (TST) and greater night-to-night variability in rapid eye movement (REM) sleep duration than Aβ-negative individuals. Across the whole sample, these sleep characteristics were associated with increased Aβ deposition in widespread brain regions, but not with cognitive or psychoaffective measures.

DISCUSSION: Shorter sleep duration and greater REM sleep variability may index early AD-related brain changes, warranting longitudinal studies to establish their prognostic significance.

Trial Registration: Age-Well randomized clinical trial of the Medit-Ageing European Project. Trial registration number: EudraCT:2016-002,441-36; IDRCB:2016-A01767-44; ClinicalTrials.gov Identifier: NCT02977819

KEYWORDS
aging, Alzheimer's disease pathology, amyloid, cognition, night-to-night sleep variability, PET, psychoaffective symptoms, REM sleep, sleep

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Highlights

- Amyloid-positive older adults exhibit greater variability in rapid eye movement (REM) sleep duration.
- Sleep alterations are not linked to cognitive or psychoaffective outcomes.
- Addressing shorter sleep duration and sleep instability may reduce Alzheimer's disease (AD) risk.

1 | BACKGROUND

The accumulation of Alzheimer's disease (AD) pathology, characterized by abnormal deposition of amyloid β peptide (Aβ) and neurofibrillary tangles, begins years before clinical manifestations appear. Individuals with abnormal brain Aβ deposition, even without symptoms, are considered at risk for progression to AD[1] and represent a population of interest for preventive interventions.

Sleep and circadian disturbances are highly prevalent in AD patients, and may appear years before clinical symptoms manifest.[2] These disturbances notably include reduced and more fragmented nocturnal sleep, increased sleep latency and wake after sleep onset, along with reduced sleep efficiency and slow wave sleep (SWS or N3 sleep).[2–4] Additionally, rapid eye movement (REM) sleep shows specific alterations notably related to the dysfunction of cholinergic neurotransmission.[5,6] Importantly, growing evidence supports a bidirectional relationship between sleep and neurodegeneration. Sleep disturbances may not only result from neuronal and synaptic alterations in sleep-regulating brain regions, but also contribute to AD pathology, notably by favoring the cerebral accumulation of neurotoxic metabolites, such as the Aβ peptide. This accumulation may occur through increased production and/or decreased glymphatic clearance.[2,7] Various sleep parameters have been associated with amyloid deposition in cognitively unimpaired older individuals, including self-reported sleep difficulties, altered sleep architecture (e.g., shorter sleep duration, sleep fragmentation) and microstructure (e.g., lower slow wave activity during non-REM sleep, and REM sleep theta power).[8–11] In this context, sleep disturbances are increasingly recognized as predictive of AD risk, pathology, and cognitive decline.[2,7,12–15] In addition, sleep disturbances in AD have been associated with behavioral and neuropsychiatric symptoms, such as depression and anxiety.[16] Notably, sleep disturbances, anxious–depressive symptoms, and Aβ may interact in a negative feedback loop from the early stages of the AD continuum, driving tau accumulation, neurodegeneration, and subsequent cognitive decline.[17]

Nevertheless, several inconsistencies in the literature limit our ability to draw firm conclusions about the associations between sleep disturbances and early AD pathology, and the clinical consequences of such disturbances remain poorly understood. For example, a recent study of five large pooled cohorts failed to establish an association between standard measures of sleep architecture (e.g., sleep stage duration, sleep efficiency, slow wave activity) and the risk of incident dementia.[18] Discrepancies across studies may, at least in part, be attributed to the variety of sleep disturbances measured, the diversity of study populations in terms of disease severity, and methodological limitations. Indeed, heterogeneous assessment methods are used to characterize sleep quality and continuity. These include subjective assessments, which do not always reflect objective sleep measures; actigraphy data, which usually monitors rest/activity cycles averaged over several days but does not provide information about sleep stages; or single-night polysomnography measurements, which can be affected by setting-related factors. A recent Delphi consensus study conducted by the *Sleep and Circadian Rhythms Professional Interest Area* of the International Society to Advance Alzheimer's Research and Treatment (ISTAART) and international experts[19] recommended prioritizing more continuous assessments of sleep and identified night-to-night sleep variability as a highly relevant aspect of sleep on which future research should focus. Indeed, greater variability in sleep patterns (e.g., sleep fragmentation) has been linked to AD risk, underlying pathology (including Aβ burden), and cognitive impairment.[20–25] Yet, no study has specifically examined the night-to-night variability in sleep stages. The emergence of ecological sleep-tracking technologies provides a unique opportunity to address this gap, by enabling multi-night, at-home recordings of sleep architecture. Such devices allow the investigation of the intra-individual variability of sleep metrics in relation to early AD pathophysiological processes.

The objectives of the current study were thus to (i) identify changes in mean levels and night-to-night variability of sleep architecture in cognitively unimpaired older adults with cerebral amyloid deposition, (ii) map the regional associations between these sleep metrics and amyloid burden, and (iii) explore their associations with cognitive and psychoaffective outcomes.

2 | METHODS

2.1 | Participants

The present study was conducted using data from the baseline visit of the Age-Well randomized controlled trial (RCT) of the Medit-Ageing European project, sponsored by the French National Institute of Health and Medical Research (INSERM). The Age-Well RCT was approved by the ethics committee (CPP Nord-Ouest III, Caen; trial registration number: EudraCT: 2016-002441-36; IDRCB: 2016-A01767-44; Clinicaltrials.gov Identifier: NCT02977819). All participants provided written informed consent prior to the examinations.

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RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources (e.g., PubMed). Growing evidence suggests a bidirectional relationship between sleep disturbances and early Alzheimer's disease (AD) pathology. However, several inconsistencies persist across studies, and some critical aspects of sleep, such as night-to-night variability of sleep parameters, are largely understudied.
2. **Interpretation**: Cognitively unimpaired older adults who were amyloid-positive exhibited shorter sleep duration and greater night-to-night variability in rapid eye movement (REM) sleep duration, compared to amyloid-negative individuals. However, these sleep alterations were not associated with cognitive or psychoaffective outcomes. They may represent early markers of AD pathological processes.
3. **Future directions**: Investigating the directionality of the association between alterations in sleep duration, night-to-night stability in sleep architecture and AD progression is crucial for determining whether interventions targeting sleep duration and stability could help prevent dementia.

Participants were enrolled between November 24, 2016, and March 5, 2018. Detailed biological, behavioral, neuroimaging, and sleep data were collected in Caen, France. The protocol and eligibility criteria have been previously described.[26] Briefly, participants were 65 years or older, community-dwelling, native French speakers, retired for at least 1 year, had a minimum of 7 years of formal education, and performed within the normal range for their age and educational level on standardized cognitive tests. The main exclusion criteria included safety concerns related to magnetic resonance imaging (MRI) or positron emission tomography (PET), evidence of a major neurological or psychiatric disorder (including substance use disorder), history of cerebral disease, presence of a chronic disease or acute unstable illness, and current or recent medication that may interfere with cognitive functioning. Two participants were excluded from all secondary analyses by the Trial Steering Committee for not meeting the eligibility criteria (i.e., history of head trauma and diagnosis of amyotrophic lateral sclerosis during the study [likely in a subclinical state at inclusion]).

At baseline, and within a maximum period of 3 months, participants underwent a structural MRI, a Florbetapir PET scan, apolipoprotein E (*APOE*) genotyping, in-home polysomnography (PSG), and a sleep recording using the Somno-Art wearable device for up to seven consecutive nights, as well as neuropsychological and psychoaffective assessments.

2.2 | Neuroimaging data acquisition and analysis

Participants underwent structural MRI and ^{18}F-Florbetapir (AV45, Amyvid) PET scans at the Cyceron Center (Caen, France), using a Philips Achieva 3T Scanner and a Discovery RX VCT 64 PET-CT scanner (General Electric Healthcare), respectively. Details on data acquisition and processing have been previously described.[27] Briefly, T1-weighted anatomical images were acquired using a 3D fast-field echo sequence (3D-T1-FFE sagittal, repetition time [TR] = 7.1 ms, echo time [TE] = 3.3 ms, flip angle = 6°, 180 slices with no gap, slice thickness = 1 mm, field of view [FoV] = 256 × 256 mm^2, in-plane resolution = 1 × 1 mm^2), segmented using fluid attenuated inversion recovery images (3D-IR sagittal, TR = 4800 ms, TE = 272 ms, inversion time (TI) = 1650 ms, flip angle = 40°, 180 slices with no gap, slice thickness = 1 mm, FoV = 250 × 250 mm^2, in-plane resolution = 0.98 × 0.98 mm^2), spatially normalized to the Montreal Neurological Institute (MNI) template, and modulated using the SPM12 segmentation procedure.

A transmission scan was performed for attenuation correction prior to PET acquisition. A 10-min PET scan, beginning 50 min after the intravenous injection of ~4 MBq/Kg of ^{18}F-Florbetapir (resolution = 3.76 × 3.76 × 4.9 mm^3, FoV = 157 mm, voxel size = 1.95 × 1.95 × 3.27 mm^3), was then acquired to reflect amyloid deposition.

PET data were co-registered with individual T1-weighted MRI scans, voxel-wise corrected for partial volume effects (PVE) using the two-compartmental voxel-wise Müller-Gärtner method,[28] and spatially normalized to the MNI template using deformation parameters derived from the T1-weighted segmentation procedure. Images were then quantitatively scaled using cerebellar gray matter as a reference, resulting in standardized uptake value ratio (SUVR) images. A smoothing kernel of 10 mm Gaussian filter was applied and images were masked to exclude non-gray matter voxels from the analyses.

Amyloid uptake was extracted and averaged across the typical regions with high amyloid load in AD, including the frontal, temporal and parietal cortices and precuneus.[29] SUVRs were then converted to the Centiloid scale following the standardized procedure of Klunk et al.[29] adapted for Florbetapir SUVRs.[30] Based on previous work,[31] a threshold of 12 Centiloids was applied to dichotomize participants as Aβ-positive (Aβ+) or Aβ-negative (Aβ−) (details in Supplementary Methods).

2.3 | Sleep measures

Sleep was monitored at home for 3 to 7 nights (mean number of nights: 4.5 ± 0.8) using the Somno-Art wearable device (Generation 1; https://www.somno-art.com/). This armband records synchronized estimates of heart rate and movement quantification (actigraphy) during a sleep allocated period of at least 5 hours. Somno-Art Software v.2.4.0 [2.4.1] was used to analyze heart rate estimates (with beat-to-beat resolution) and actigraphy signals (with 1-Hz resolution),

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providing sleep stage classification at a 1-second epoch resolution. The latter classification was resampled in 30-second epochs, selecting the dominant stage (or the first stage to appear if stages were equally represented). The sleep classification algorithm is based on expert rules associated with Support Vector Machine (SVM) detectors. Further information on the data processing methodology is available in Muzet et al.[32] The main exclusion criteria for the recordings were no or incorrect use of the device (e.g., device removal), failure to import data, time-stamping issues, invalid recordings for software analysis (i.e., bad actigraphy and/or heart rate signals), exclusion from quality control (e.g., time in bed less than 5 hours), or less than three valid recordings available for one individual. Somno-Art Software has been validated against PSG visual scoring in healthy young to middle-aged adults and patients with insomnia, obstructive sleep apnea, and major depressive disorder.[32,33] We evaluated the performance of Somno-Art Software in an elderly population, by conducting comparison analyses between Somno-Art Software classification and PSG visual scoring in a subsample of the Age-Well RCT with matching Somno-Art and PSG recordings. The detailed methodology and outcomes are available in Supplementary Methods. Briefly, the discrepancy analysis revealed a proportional bias for all parameters, the magnitude of the bias depending on the PSG-derived measures (Table S1). Bland-Altman plots are displayed in Figure S1. Regarding Wake/Sleep classification, the epoch-by-epoch analysis revealed that Somno-Art Software exhibited 91% sensitivity (i.e., ability to correctly classify PSG sleep epochs) and 54% specificity (i.e., ability to correctly classify PSG wake epochs), with a "substantial" agreement between measurements (prevalence-adjusted bias-adjusted kappa (PABAK): 0.64). For the four-stage classification, agreement between the two methods ranged from "fair" for N1+N2 (PABAK: 0.28) to "substantial" for Wake (PABAK: 0.64), N3 (PABAK: 0.72), and REM (PABAK: 0.68) stages. A proportional error matrix between the two methods is presented in Table S2 and additional epoch-by-epoch metrics are provided in Table S3.

Several metrics reflecting sleep architecture and continuity were derived from the sleep stage classification: total sleep time (TST, minutes; corresponding to the total duration of non-wake epochs), sleep onset latency (SOL, minutes; corresponding to the time from lights-off to the first sleep epoch), wake after sleep onset (WASO, minutes; corresponding to the duration of wake epochs after sleep onset), sleep efficiency (SE, percentage; corresponding to the ratio between TST and time in bed), the duration of N1, N2, N3, and REM sleep stages (expressed in minutes and as a percentage of TST), and REM sleep latency (REML, minutes; corresponding to the duration between sleep onset and the first epoch of REM sleep). For each parameter, mean and night-to-night variability measures were calculated. The intra-individual variability (IIV) of sleep parameters was characterized using an intra-individual coefficient of variation, computed as the standard deviation divided by the mean, multiplied by 100. This mean-referenced measure of variability accounts for the greater likelihood of higher variability in individuals with higher mean scores.[23,34–36]

Additionally, self-reported sleep quality and disturbances, as well as insomnia symptoms, were assessed using the Pittsburgh Sleep Quality Index (PSQI)[37] and the Insomnia Severity Index (ISI),[38] respectively.

2.4 | Cognitive and psychoaffective measures

All participants underwent a detailed neuropsychological assessment, providing a number of scores reflecting global functioning, episodic and working memory and various executive functions such as inhibition, flexibility, and processing speed. We used those scores to create four cognitive composite scores targeting cognitive domains typically affected in aging and early AD: the Preclinical Alzheimer's Cognitive Composite 5 (PACC-5), verbal episodic memory, executive functioning, and attention/speed (see Supplementary Methods,[26]). Additionally, subjective cognitive difficulties were evaluated with the Cognitive Difficulties Scale (CDS).[39] Two subscores were obtained from the CDS: (1) a reduced score reflecting global cognitive difficulties, and (2) a score specifically reflecting memory difficulties, with higher values indicating greater perceived difficulties (details in Supplementary Methods).

Psychoaffective measures included the 15-item version of the Geriatric Depression Scale (GDS)[40] to highlight subclinical depressive symptoms, and the Form Y-B of the State-Trait Anxiety Inventory (STAI-B)[41] to assess trait anxiety symptoms. In addition, two complementary aspects of repetitive negative thinking were measured: (1) brooding (i.e., past-directed negative thoughts) and (2) worry (i.e., future-directed negative thoughts), respectively assessed using the Brooding subscore of the Rumination Response Scale (RRS)[42] and the total score of the Penn State Worry Questionnaire (PSWQ).[43] Higher scores on these psychoaffective questionnaires indicate greater severity of symptoms (details in Supplementary Methods).

2.5 | Statistical analyses

Statistical analyses were performed using R (version 4.4.2; http://www.r-project.org) and SPM12. Differences between groups for demographics and subjective sleep measures according to Aβ status were assessed using non-parametric Wilcoxon rank-sum test for continuous variables and chi-squared statistics (or a non-parametric Fisher's exact test) for categorical variables. For all analyses, statistical significance was set to $p < 0.05$, except for voxel-wise multiple regressions. For the latter, results were considered significant at a $p < 0.005$ (uncorrected) threshold, with a minimal cluster size of $k = 100$ voxels.

To identify sleep characteristics altered in cognitively unimpaired older individuals with cerebral amyloid deposition, all sleep parameters were compared between Aβ– and Aβ+ participants using type II analyses of covariance (ANCOVAs), with Aβ status (based on an amyloid-positivity 12-Centiloid threshold) as the between-participants factor and sleep metrics as the dependent variables. For models that did not meet the conditions for ANCOVA, robust ANCOVA models were additionally performed using *lmrob* function. Additionally, secondary comparison analyses were conducted using a more conservative amyloid-positivity threshold of 25 Centiloids,[44] to ensure that our findings were not driven by potential misclassification at lower Centiloid values. To assess whether the findings extended beyond group differences, additional linear regression models were also fitted

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to the entire sample, using continuous global cortical amyloid burden (Centiloid values) as the independent variable.

Then, to characterize the cerebral topography of the associations between these Aβ-related sleep metrics and Aβ deposition, voxel-wise multiple regression analyses were performed between each Aβ-related sleep metric and amyloid load obtained from PET images.

Lastly, we assessed the associations between Aβ-related sleep metrics and cognitive and psychoaffective outcomes by conducting multiple regression analyses with cognitive and psychoaffective measures as dependent variables and sleep metrics as independent predictors. Robust linear regressions were performed to confirm the results of models that did not meet the conditions for multiple linear regression.

All analyses were adjusted for age, sex, education level, and the Apnea–Hypopnea Index (AHI) obtained from a polysomnography recording performed as part of the protocol. For significant results, secondary sensitivity analyses were performed by additionally controlling for *APOE* ε4 status (i.e., carrying at least one copy of the ε4 allele) and the number of recorded nights.

3 | RESULTS

3.1 | Sample characteristics

Of the 135 participants enrolled in the Age-Well RCT at baseline, 76 underwent sleep assessments and neuroimaging scans, neuropsychological and psychoaffective examinations, as well as blood sampling for *APOE* ε4 genotyping, and were included in the final analysis sample (flow diagram in Figure 1). Their characteristics are described in Table 1. The study sample consisted of cognitively unimpaired older adults with an average age of 69.1 ± 3.4 years, 63.2% female, 22.4% *APOE* ε4 carriers, and an average education level of 12.8 ± 3.0 years. Fifty-four individuals were Aβ−, and 22 were Aβ+. There were no significant differences between the two groups in terms of age, sex ratio, education level, Mini-Mental State Examination (MMSE) score, body mass index (BMI), number of recorded nights, proportion of *APOE* ε4 carriers, or current use of sleep medication (i.e., on a regular basis (≥1/week), as determined by the PSQI item about sleep medication use during the last month). As expected, the Aβ+ group displayed a greater Centiloid value ($W = 1188$; $p < 0.001$). Additionally, Aβ+ participants exhibited higher AHI values ($W = 843.5$; $p = 0.004$). Interestingly, no differences were observed between groups in terms of subjective sleep quality or the severity of insomnia symptoms, as assessed by the PSQI and the ISI, respectively. The descriptive characteristics of participants' sleep metrics are presented in Table 2, and a correlation matrix between all sleep metrics (mean and variability) is provided in Figure S2.

3.2 | Differences in sleep architecture according to Aβ status

When comparing sleep parameters between the two groups (Aβ+ vs. Aβ−) using ANCOVAs (Table 3), adjusting for age, sex, education, and the AHI, Aβ+ individuals exhibited shorter TST ($F = 4.85$, $p = 0.031$, $\eta_p^2 = 0.06$) and greater night-to-night variability of REM sleep duration (REM-IIV, minutes: $F = 5.31$, $p = 0.024$, $\eta_p^2 = 0.07$; REM-IIV, percentage: $F = 4.07$, $p = 0.048$, $\eta_p^2 = 0.05$). Results remained unchanged with robust ANCOVAs for models that did not meet criteria for ANCOVA (Table S4). No other significant differences were observed.

Sensitivity analyses showed that, when considering a more conservative amyloid-positivity 25-Centiloid threshold, these sleep parameters remained statistically different between Aβ− and Aβ+ individuals (TST: $F = 6.34$, $p = 0.014$, $\eta_p^2 = 0.08$; REM-IIV, minutes: $F = 8.35$, $p = 0.005$, $\eta_p^2 = 0.11$; REM-IIV, percentage: $F = 5.73$, $p = 0.019$, $\eta_p^2 = 0.08$; Table S5). However, it should be noted that, in this case, the Aβ+ group is very small ($n = 12$), so the results should be interpreted with caution. Results remained unchanged with robust ANCOVA for the model that did not meet criteria for ANCOVA (Table S6). When considering continuous measures of global cortical amyloid burden (Centiloid value) across the entire sample, the results revealed a significant association between amyloid deposition and variability in REM sleep duration, expressed in minutes (REM-IIV, minutes; $\beta = 0.137$, $p = 0.005$), suggesting that higher amyloid load is associated with greater variability in REM sleep duration (Table S7). Sensitivity analyses (Tables S8 and S9) also showed similar results for TST and the variability of REM sleep duration expressed in minutes (REM-IIV, minutes), when additionally controlling for *APOE* ε4 status (TST: $F = 5.91$, $p = 0.018$, $\eta_p^2 = 0.08$; REM-IIV, minutes: $F = 5.77$, $p = 0.019$, $\eta_p^2 = 0.08$) and the number of recorded nights (TST: $F = 4.47$, $p = 0.038$, $\eta_p^2 = 0.06$; REM-IIV, minutes: $F = 4.51$, $p = 0.037$, $\eta_p^2 = 0.06$). However, greater variability of REM sleep duration, expressed as a percentage of TST (REM-IIV, percentage), observed in Aβ+ individuals, was no longer significant after additionally controlling either for *APOE* ε4 status ($F = 3.96$, $p = 0.050$, $\eta_p^2 = 0.05$) or the number of recorded nights ($F = 3.04$, $p = 0.085$, $\eta_p^2 = 0.04$). Results of sensitivity analyses remained unchanged with robust ANCOVA for the model that did not meet criteria for ANCOVA (Table S10).

3.3 | Topography of the associations between Aβ-related sleep metrics and cerebral Aβ deposition

We then assessed the associations between sleep metrics found to be significantly altered in Aβ+ individuals (i.e., TST and the variability of REM sleep duration) and the regional topography of Aβ deposition using voxel-wise multiple regressions, adjusting for age, sex, education, and the AHI. The results of significant voxel-wise regressions are presented in Figure 2, and detailed peak statistics and coordinates of significant clusters are reported in Table 4.

TST was negatively associated with Aβ deposition across several medial and lateral parietal and occipital areas, including the cuneus and precuneus, and lateral temporal cortex. The variability of REM sleep duration, expressed in minutes (REM-IIV, minutes), was positively associated with Aβ deposition in widespread brain regions. A large significant cluster notably encompassed bilateral temporal and posterior regions, including the precuneus, cuneus, and posterior cingulate. Additional significant clusters were found in frontal and parietal areas,

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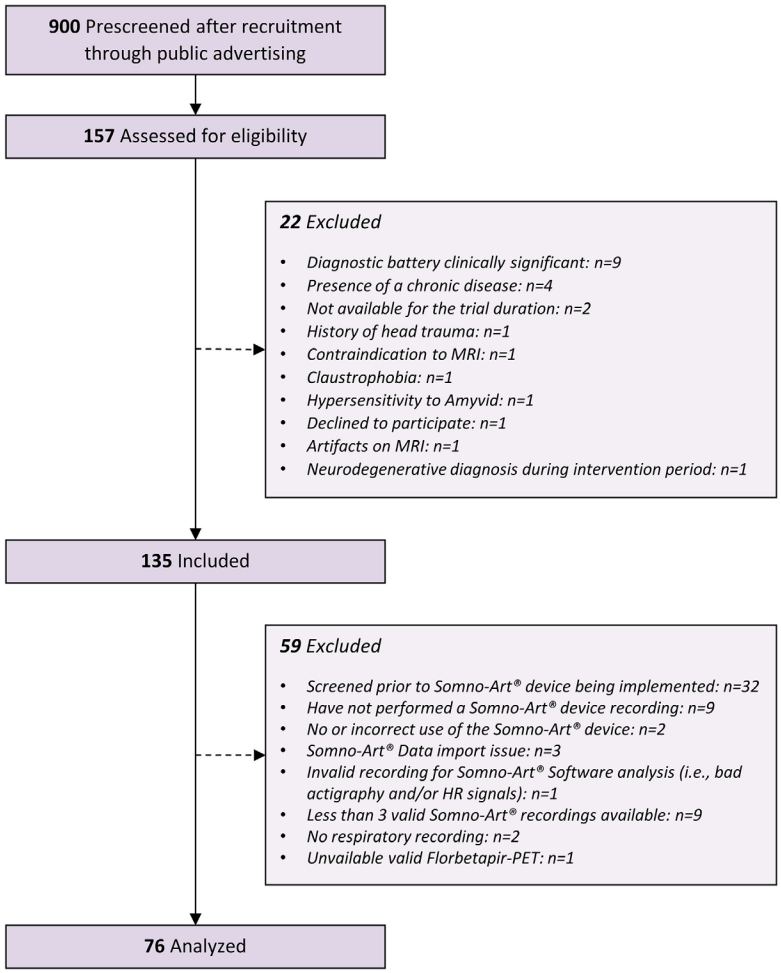


FIGURE 1 Flow diagram of the inclusion process. HR, heart rate; MRI, magnetic resonance imaging; PET, positron emission tomography.

TABLE 1 Participants' characteristics.

Characteristic	Total sample ($n = 76$)	Aβ− ($n = 54$)	Aβ+ ($n = 22$)	*p*-value for between-group differences
Age (years)	69.1 ± 3.4 [65.0; 79.0]	68.8 ± 3.2 [65.0; 77.6]	69.6 ± 4.0 [65.0; 79.0]	0.499
Women, n (%)	48 (63.2)	34 (62.9)	14 (63.6)	0.956
Education (years)	12.8 ± 3.0 [7; 20]	12.9 ± 3.0 [7; 17]	12.7 ± 3.2 [7; 20]	0.758
MMSE total score	29.0 ± 1.1 [26; 30]	29.1 ± 1.0 [26; 30]	28.9 ± 1.1 [27; 30]	0.391
BMI (kg/m^2)	25.7 ± 3.9 [18.1; 37.2]	25.6 ± 3.8 [18.1; 37.2]	26.1 ± 4.1 [20.4; 33.9]	0.762
Current sleep medication use, n (%)[a]	3 (4.0)	3 (5.6)	0 (0.0)	0.552
AHI (n/h)	25.3 ± 14.1 [2.4; 75.5]	22.0 ± 11.6 [2.4; 60.5]	33.5 ± 16.9 [10.4; 75.5]	**0.004**
APOE ε4 carriers, n (%)	17 (22.4)	10 (18.5)	7 (31.8)	0.234
Centiloid value	9.0 ± 26.0 [−22.0; 101.3]	−3.6 ± 8.8 [−22.0; 11.8]	40.1 ± 28.1 [12.1; 101.3]	**<0.001**
PSQI total score	4.9 ± 3.3 [0; 12]	4.8 ± 3.4 [0; 12]	5.0 ± 3.2 [1; 12]	0.652
ISI total score	6.9 ± 5.2 [0; 20]	6.4 ± 4.8 [0; 19]	8.1 ± 6.0 [1; 20]	0.307
Number of Somno-Art recorded nights	4.5 ± 0.8 [3; 7]	4.6 ± 0.7 [3; 6]	4.3 ± 1.1 [3; 7]	0.285

Note: Data are presented as mean ± SD [minimum; maximum] for continuous variables or n (%) for categorical variables. Differences between groups for demographics and subjective sleep measures according to Aβ status were assessed using non-parametric Wilcoxon rank-sum test for continuous variables and chi-square statistics (or a non-parametric Fisher's exact test) for categorical variables. Results in bold indicate significant differences at the $p < 0.05$ level.
Abbreviations: %, percentage; AHI, Apnea–Hypopnea Index; APOE ε4, ε4 allele of the apolipoprotein E; Aβ, amyloid β; BMI, body mass index; h, hour; ISI, Insomnia Severity Index; MMSE, Mini-Mental State Examination; n, number; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.
[a]Use of sleep medication on a regular basis (≥1/week), as determined by the PSQI item about sleep medication use during the last month.

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TABLE 2 Descriptive characteristics of sleep mean and variability metrics.

Sleep parameter	Mean value	IIV (%)
TST (min)	395.0 ± 54.0 [231.7; 501.3]	11.4 ± 5.3 [3.0; 30.1]
SOL (min)	19.4 ± 12.4 [1.2; 75.7]	68.3 ± 29.6 [15.8; 153.8]
WASO (min)	69.9 ± 37.7 [23.4; 227.0]	36.8 ± 18.1 [3.0; 99.8]
SE (%)	81.7 ± 8.0 [48.6; 92.1]	7.0 ± 4.1 [1.7; 22.2]
N1 (min)	35.2 ± 8.3 [15.7; 64.8]	18.6 ± 7.5 [2.8; 40.2]
N1 (%)	9.2 ± 2.7 [4.0; 17.3]	18.6 ± 7.4 [5.4; 47.4]
N2 (min)	216.6 ± 35.6 [114.8; 320.7]	16.1 ± 7.7 [3.3; 40.1]
N2 (%)	54.9 ± 6.0 [41.4; 68.6]	10.9 ± 5.1 [3.5; 31.6]
N3 (min)	68.2 ± 30.2 [4.7; 162.1]	37.7 ± 19.2 [4.8; 89.3]
N3 (%)	17.1 ± 6.7 [1.5; 33.7]	36.1 ± 17.9 [11.0; 83.2]
REM (min)	75.0 ± 18.6 [33.9; 115.1]	23.6 ± 11.5 [5.5; 56.7]
REM (%)	18.9 ± 3.4 [10.9; 25.1]	20.5 ± 10.1 [2.7; 48.5]
REML (min)	86.5 ± 29.5 [43.2; 174.0]	41.4 ± 20.4 [8.4; 88.4]

Note: Data are presented as mean ± SD [minimum; maximum]. Intra-individual coefficients of variation are computed as the standard deviation of the sleep metric divided by the mean, multiplied by 100.
Abbreviations: %, percentage; IIV, intra-individual variability; min, minutes; REM, rapid eye movement sleep; REML, rapid eye movement sleep latency; SD, standard deviation; SE, sleep efficiency; SOL, sleep onset latency; TST, total sleep time; WASO, wake after sleep onset.

TABLE 3 Comparisons of sleep mean and variability metrics between Aβ− and Aβ+ individuals.

Sleep parameter	Df	Aβ− adjusted mean [95% CI]	Aβ+ adjusted mean [95% CI]	F	*p*-value	η_p^2
Mean sleep metrics						
TST (min)	1	397.1 [383.8, 410.4]	369.0 [347.8, 390.2]	4.85	**0.031**	0.065
SOL (min)	1	20.5 [17.0, 24.1]	17.8 [12.2, 23.5]	0.65	0.423	0.009
WASO (min)	1	72.5 [62.5, 82.5]	68.8 [52.7, 84.9]	0.15	0.700	0.002
SE (%)	1	81.1 [78.9, 83.2]	81.1 [77.7, 84.5]	0.00	1.00	6.414×10^{-10}
N1 (min)	1	36.1 [33.9, 38.4]	34.0 [30.4, 37.5]	1.01	0.318	0.014
N1 (%)	1	9.4 [8.7, 10.1]	9.5 [8.5, 10.6]	0.04	0.834	6.309×10^{-4}
N2 (min)	1	218.7 [209.0, 228.5]	201.8 [186.2, 217.4]	3.27	0.075	0.045
N2 (%)	1	55.3 [53.6, 57.0]	54.4 [51.7, 57.1]	0.28	0.596	0.004
N3 (min)	1	67.0 [59.1, 75.0]	63.6 [50.9, 76.4]	0.20	0.659	0.003
N3 (%)	1	16.5 [14.7, 18.4]	17.4 [14.5, 20.3]	0.24	0.628	0.003
REM (min)	1	75.2 [70.3, 80.2]	69.6 [61.8, 77.5]	1.42	0.237	0.020
REM (%)	1	18.8 [17.8, 19.7]	18.7 [17.2, 20.2]	0.02	0.892	2.641×10^{-4}
REML (min)	1	87.4 [78.9, 95.9]	81.4 [67.8, 95.0]	0.54	0.466	0.008
IIV (%) sleep metrics						
TST (min)	1	11.2 [9.8, 12.6]	13.2 [10.9, 15.5]	2.15	0.147	0.030
SOL (min)	1	66.5 [58.6, 74.4]	68.9 [56.3, 81.5]	0.10	0.750	0.001
WASO (min)	1	36.4 [31.5, 41.4]	32.9 [24.9, 40.8]	0.57	0.454	0.008
SE (%)	1	7.5 [6.3, 8.6]	6.5 [4.6, 8.3]	0.76	0.387	0.011
N1 (min)	1	19.0 [16.9, 21.1]	16.5 [13.1, 19.9]	1.46	0.232	0.020
N1 (%)	1	19.7 [17.6, 21.7]	15.9 [12.5, 19.2]	3.66	0.060	0.050
N2 (min)	1	15.7 [13.6, 17.9]	18.6 [15.2, 22.1]	2.01	0.161	0.028

(Continues)

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TABLE 3 (Continued)

Sleep parameter	Df	Aβ− adjusted mean [95% CI]	Aβ+ adjusted mean [95% CI]	F	*p*-value	η_p^2
N2 (%)	1	10.6 [9.1, 12.0]	11.8 [9.4, 14.1]	0.74	0.394	0.010
N3 (min)	1	39.2 [33.9, 44.5]	36.2 [27.8, 44.7]	0.35	0.557	0.005
N3 (%)	1	37.4 [32.5, 42.3]	35.3 [27.4, 43.1]	0.21	0.649	0.003
REM (min)	1	22.2 [19.2, 25.3]	28.9 [24.1, 33.7]	5.31	**0.024**	0.070
REM (%)	1	18.9 [16.1, 21.7]	24.3 [19.8, 28.7]	4.07	**0.048**	0.055
REML (min)	1	40.5 [34.6, 46.5]	43.3 [33.8, 52.9]	0.24	0.629	0.003

Note: Results of type II ANCOVAs performed with each sleep parameter as the dependent variable, Aβ status as the between-participants factor, and age, sex, education, and AHI as covariates. Results in bold indicate significant differences at the $p < 0.05$ level.
Abbreviations: %, percentage; AHI, Apnea–Hypopnea Index; Aβ, amyloid β; ANCOVA, analysis of covariance; CI, confidence interval; Df, degrees of freedom; IIV, intra-individual variability; min, minutes; REM, rapid eye movement sleep; REML, rapid eye movement sleep latency; SE, sleep efficiency; SOL, sleep onset latency; TST, total sleep time; WASO, wake after sleep onset; η_p^2, partial eta squared.

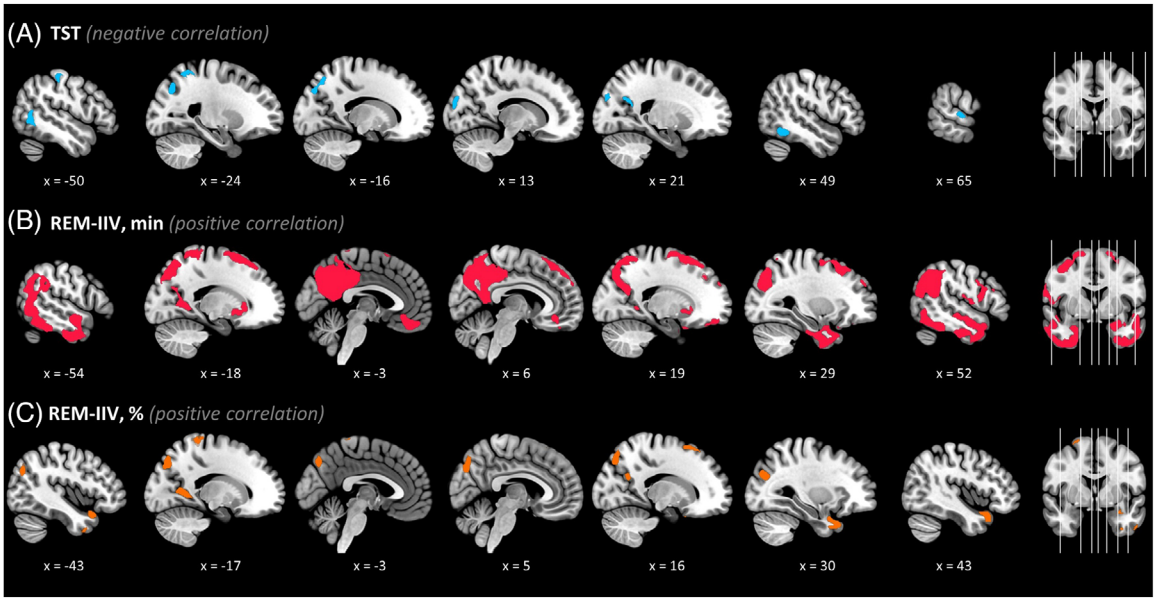


FIGURE 2 Neuroimaging patterns of significant associations between Aβ-related sleep metrics and amyloid deposition. Results of voxel-wise multiple regressions showing significant associations between (A) TST, variability in REM sleep duration expressed in (B) minutes (REM-IIV, minutes), and (C) as a percentage of TST (REM-IIV, percentage) and amyloid deposition. Results are presented at the $p < 0.005$ (uncorrected) threshold, combined with a minimal cluster size of $k = 100$ voxels, controlling for age, sex, education, and AHI. %, percentage; Aβ, amyloid β; AHI, Apnea–Hypopnea Index; IIV, intra-individual variability; min, minutes; REM, rapid eye movement sleep; TST, total sleep time.

as well as subcortical regions (e.g., amygdala, pallidum). Of note, the associations observed in the main cluster and in the right frontal and precentral regions, survived a family-wise error (FWE) cluster-level correction. When REM sleep duration was expressed as a percentage of TST (REM-IIV, percentage), its variability was associated with Aβ deposition in smaller clusters, mostly medial and lateral temporal areas and the precuneus, largely corresponding to subregions of the widespread associations observed with variability of REM sleep duration expressed in minutes (REM-IIV, minutes).

Overall, sensitivity analyses showed broadly consistent results after additional adjustment for *APOE* ε4 status (Table S11). After further adjusting for the number of recorded nights, the associations between TST and Aβ burden remained largely unchanged. Associations with REM sleep variability expressed in minutes (REM-IIV, minutes) were observed in the same regions, though to a lesser extent, and some of the associations with REM sleep variability expressed as a percentage of TST (REM-IIV, percentage) were no longer significant (Table S12).

3.4 | Associations between Aβ-related sleep metrics and cognitive and psychoaffective outcomes

Lastly, multiple regression analyses were used to explore the associations between each Aβ-related sleep metric and cognitive and

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TABLE 4 Significant associations between Aβ-related sleep metrics and amyloid deposition.

Sleep parameter	Cor	Brain regions	No. of voxels	MNI coordinates x	y	z	t-value	$p_{FWE\text{-}corrected}$
TST (min)	–	R cuneus, occipital sup	380	14	−88	20	4.46	
		L postcentral, parietal inf	122	−51	−26	54	3.66	
		R temporal sup, rolandic oper	117	68	−14	6	3.40	
		L parietal sup/inf, postcentral	257	−24	−51	58	3.40	
		L temporal mid/inf, occipital mid	426	−50	−58	−2	3.33	
		R precuneus, cuneus, calcarine	107	24	−60	24	3.30	
		L parietal sup/inf, occipital sup/mid, cuneus, precuneus	590	−16	−81	36	3.27	
		R temporal inf, fusiform	274	50	−54	−15	3.26	
		R occipital mid/sup	154	33	−75	26	3.18	
REM-IIV, min (%)	+	RL precuneus, cuneus, temporal sup/mid/inf, temporal pole sup/mid, cingulate post/mid, parahippocampal, parietal sup/inf, angular, supramarginal, occipital sup/mid/inf, calcarine, fusiform, lingual, postcentral, paracentral lobule, amygdala R insula, frontal inf orb, OFC post/med, hippocampus	50,662	−50	6	−40	4.91	<0.001
		R frontal sup/mid/sup med/inf oper, supp motor area, precentral	4497	18	14	60	3.88	0.037
		R postcentral, precentral, rolandic oper, frontal inf oper/inf tri, temporal sup, supramarginal	1647	66	−9	2	3.73	
		L insula, frontal inf tri	277	−27	21	8	3.59	
		L putamen, caudate, pallidum, olfactory	437	−24	16	2	3.50	
		L frontal sup/sup med/mid, supp motor area, precentral	1392	−15	10	66	3.46	
		RL rectus, frontal med orb, OFC med, ACC sub	1259	−4	39	−2	3.21	
		L frontal sup/mid	168	−26	52	4	3.13	
		R putamen, caudate, vent str, pallidum	243	18	20	−3	3.00	
		R OFC ant/med, frontal sup/mid	256	21	51	−16	2.99	
REM-IIV, % (%)	+	R temporal pole sup/mid, parahippocampal, amygdala, OFC post	1263	28	12	−33	4.85	
		L temporal pole sup/mid, parahippocampal, amygdala, temporal mid/inf, fusiform	1248	−44	20	−21	3.70	
		L calcarine, lingual, precuneus	583	−20	−54	3	3.68	
		RL precuneus, cuneus R parietal sup	775	16	−75	52	3.67	
		L precuneus, cuneus, parietal sup, occipital sup	609	−16	−76	44	3.42	
		L postcentral, parietal sup, precuneus, paracentral lobule	375	−22	−45	70	3.39	
		R precuneus	146	21	−58	27	3.28	
		R OFC post/med, frontal inf orb, insula	125	21	14	−27	3.24	
		R frontal sup/sup med, supp motor area	504	16	26	62	3.24	
		R temporal mid/sup,	244	70	−30	−6	3.21	
		R occipital mid/sup	235	30	−75	26	3.20	
		L angular, occipital mid	173	−42	−72	30	2.94	

Note: Results of voxel-wise multiple regressions analyses performed between each Aβ-related sleep metric (i.e., TST, REM-IIV, minutes, and REM-IIV, percentage), separately, and Aβ load, controlling for age, sex, education, and AHI. Results are presented at the $p < 0.005$ (uncorrected) threshold, with a minimal cluster size of $k = 100$ voxels. *p*-v-alues after FWE cluster-level correction are indicated when significant. The first region mentioned corresponds to the statistical peak, and the other regions listed compose the rest of each cluster. T-values and coordinates are indicated for the peak of each cluster.

Abbreviations: %, percentage; −, negative correlation; +, positive correlation; ACC, anterior cingulate cortex; AHI, Apnea–Hypopnea index; ant, anterior; Aβ, amyloid β; Cor, correlation; FWE, family-wise error; IIV, intra-individual variability; inf, inferior; L, left; med, medial; mid, middle; min, minutes; MNI, Montreal Neurological Institute; No., number; OFC, orbitofrontal cortex; oper, operculum; orb, orbital; post, posterior; R, right; REM, rapid eye movement sleep; sub, subgenual; sup, superior; supp motor area, supplementary motor area; tri, triangular part; TST, total sleep time; vent str, ventral striatum.

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TABLE 5 Associations between Aβ-related sleep metrics and cognitive and psychoaffective outcomes.

Predictor	Outcome	Estimate [95% CI]	Standard Error	*t*	*p*
Cognitive outcomes					
TST (min)	PACC-5	−0.001 [−0.005, 0.002]	0.002	−0.71	0.481
	Episodic memory composite	−0.002 [−0.007, 0.002]	0.002	−1.09	0.282
	Executive functioning composite	0.001 [−0.003, 0.005]	0.002	0.49	0.624
	Attention/speed composite	−0.002 [−0.006, 0.003]	0.002	−0.74	0.462
	CDS reduced score	0.043 [−0.026, 0.112]	0.034	1.25	0.216
	CDS memory score	0.022 [0.000, 0.044]	0.011	2.03	**0.046**
REM-IIV, min (%)	PACC-5	−0.001 [−0.017, 0.016]	0.008	−0.07	0.946
	Episodic memory composite	−0.004 [−0.024, 0.016]	0.010	−0.38	0.704
	Executive functioning composite	−0.008 [−0.026, 0.011]	0.009	−0.82	0.416
	Attention/speed composite	0.017 [−0.004, 0.037]	0.010	1.60	0.113
	CDS reduced score	−0.220 [−0.522, 0.082]	0.151	−1.45	0.150
	CDS memory score	−0.076 [−0.174, 0.021]	0.049	−1.56	0.124
REM-IIV, % (%)	PACC-5	0.006 [−0.012, 0.024]	0.009	0.65	0.521
	Episodic memory composite	0.001 [−0.021, 0.023]	0.011	0.12	0.901
	Executive functioning composite	−0.009 [−0.029, 0.012]	0.010	−0.86	0.393
	Attention/speed composite	0.022 [0.000, 0.044]	0.011	1.99	0.051
	CDS reduced score	−0.186 [−0.516, 0.143]	0.165	−1.13	0.263
	CDS memory score	−0.060 [−0.167, 0.047]	0.054	−1.12	0.267
Psychoaffective outcomes					
TST (min)	GDS score	0.007 [−0.003, 0.017]	0.005	1.48	0.144
	STAI-B score	0.008 [−0.028, 0.044]	0.018	0.44	0.658
	RRS brooding score	−0.004 [−0.015, 0.007]	0.006	−0.80	0.425
	PSWQ score	−0.017 [−0.072, 0.039]	0.028	−0.60	0.552
REM-IIV, min (%)	GDS score	0.028 [−0.015, 0.071]	0.022	1.28	0.204
	STAI-B score	0.018 [−0.143, 0.179]	0.081	0.22	0.826
	RRS brooding score	0.043 [−0.004, 0.091]	0.024	1.82	0.074
	PSWQ score	0.083 [−0.162, 0.329]	0.123	0.68	0.499
REM-IIV, % (%)	GDS score	0.026 [−0.021, 0.073]	0.024	1.11	0.271
	STAI-B score	0.023 [−0.152, 0.197]	0.087	0.26	0.796
	RRS brooding score	0.038 [−0.014, 0.090]	0.026	1.45	0.153
	PSWQ score	0.011 [−0.256, 0.278]	0.134	0.08	0.936

Note: Results of multiple linear regressions performed with each Aβ-related sleep metric (i.e., TST, REM-IIV, minutes, and REM-IIV, percentage) as the predictor, and cognitive and psychoaffective scores as outcomes, controlling for age, sex, education, and AHI. The result in bold indicates a significant difference at the $p < 0.05$ level.

Abbreviations: %, percentage; AHI, Apnea–Hypopnea Index; Aβ, amyloid β; CDS, Cognitive Difficulties Scale; CI, confidence interval; GDS, Geriatric Depression Scale; IIV, intra-individual variability; min, minutes; PACC-5, Preclinical Alzheimer's Cognitive Composite 5; PSWQ, Penn State Worry Questionnaire; REM, rapid eye movement sleep; RRS, Rumination Response Scale; STAI-B, Form Y-B of the State-Trait Anxiety Inventory; TST, total sleep time.

psychoaffective outcomes (Table 5), adjusting for age, sex, education and the AHI. No association was found between TST or variability of REM sleep duration and cognitive composite scores. We observed a marginal association between longer TST and higher subjective memory difficulties ($\beta = 0.02$; $p = 0.046$; Figure 3). Finally, no significant association was found between Aβ-related sleep metrics and psychoaffective outcomes. None of these results were modified using robust regressions for models that did not satisfy the conditions for regression (Table S13).

Sensitivity analyses showed that the association between TST and subjective memory difficulties remained significant after additional adjustment for *APOE* ε4 status ($\beta = 0.03$; $p = 0.026$; Table S14) or the number of recorded nights ($\beta = 0.02$; $p = 0.032$; Table S15).

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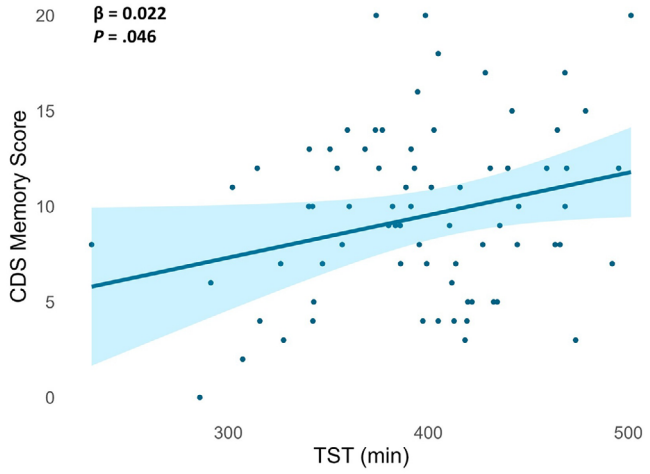


FIGURE 3 Significant association between total sleep time and subjective memory difficulties. Scatterplot illustrating the association between TST and CDS memory score, corrected for age, sex, education, and AHI. AHI, Apnea–Hypopnea Index; CDS, Cognitive Difficulties Scale; min, minutes; TST, total sleep time.

4 | DISCUSSION

This study aimed to characterize alterations in sleep architecture in cognitively unimpaired older adults according to Aβ status, using an ecological multi-night objective sleep assessment, and to examine their associations with regional amyloid deposition, cognitive and psychoaffective outcomes. Aβ+ individuals showed reduced mean TST and greater night-to-night variability of REM sleep duration, associated with amyloid deposition mainly in temporal and posterior regions, but not with objective cognitive or psychoaffective measures.

Our results corroborate previous studies showing that shorter sleep duration is linked to increased Aβ deposition.[45–47] This aligns with the hypothesis that sleep promotes Aβ clearance, while insufficient sleep may disrupt this process, contributing to Aβ accumulation.[2] Interestingly, shorter TST has also been associated with a higher risk of dementia.[48,49] However, a meta-analysis found no overall association between TST and amyloid load.[50] Heterogeneity in study design, sleep measurement, biomarker assessment, and statistical approaches may account for such discrepancies.

Beyond standard sleep metrics, our study identified greater night-to-night variability in REM sleep duration as a distinctive feature of Aβ+ individuals. Night-to-night variability is an increasingly recognized dimension of sleep health, with emerging evidence linking greater variability in several sleep metrics, such as sleep fragmentation, to amyloid deposition,[20,23] plasma and cerebrospinal fluid (CSF) AD biomarkers,[21] as well as cognitive impairment,[23] dementia risk,[25] and mortality.[51] Previous work investigating sleep variability has focused on sleep continuity metrics, such as sleep fragmentation, WASO or TST. For example, variability in sleep fragmentation and WASO during the first half of the night has been associated with amyloid deposition notably in frontal and parietal regions,[20,24] whereas variability in TST has been associated with cerebral Aβ burden or CSF and plasma p-tau/Aβ ratios in individuals with mild cognitive impairment (MCI)[23] or a parental history of sporadic AD,[21] respectively. In line with Jouvencel et al.,[24] we did not observe differences in WASO or TST variability according to Aβ status, suggesting that greater variability in sleep continuity may occur later or under specific genetic or disease vulnerability conditions. Moreover, we did not identify variability in SE as an Aβ-related sleep metric in cognitively unimpaired older individuals, contrasting with prior work showing an association between SE variability and Aβ burden in MCI, especially in *APOE* ε4 carriers.[23] Of note, these results were not confirmed in individuals with a parental history of sporadic AD.[21] These data suggest that distinct variability metrics, reflecting unstable sleep patterns, may be differentially related to amyloid pathology depending on disease stage or genetic susceptibility.

REM sleep is known to play a crucial role in memory processing, emotional regulation, neural homeostasis, and synaptic regulation.[52] Previous work suggests that reduced REM sleep duration,[53–55] longer REM sleep latency,[54,56] or alterations in REM sleep microstructure,[8] may represent early markers of AD pathology, even before dementia onset, and/or be predictive of cognitive decline and dementia risk. The mechanisms underlying REM sleep alterations likely involve early neurodegeneration within REM-regulatory networks, as core REM sleep regulatory centers (i.e., brainstem and basal forebrain cholinergic nuclei, hypothalamus) are among the earliest regions to accumulate AD-related pathology.[57–61] Recent studies suggest that resulting cholinergic denervation and neurotransmitter imbalance may compromise REM sleep integrity and stability.[5,6,62]

Moreover, circadian dysfunction observed in the early stages of AD[63] may also contribute to the night-to-night instability in REM sleep duration. The daily expression of REM sleep is modulated by circadian rhythms, and may involve both promoting and inhibitory mechanisms mediated by the suprachiasmatic nucleus and orexinergic neurons.[64] Thus, AD pathology accumulation in circadian regulating areas (e.g., suprachiasmatic nucleus in the hypothalamus)[2] may lead to irregular REM propensity and fragmentation, and inconsistent REM sleep patterns across nights. Consistently, a reduction in the circadian amplitude of REM sleep has been associated with altered microstructural integrity of the hypothalamus.[65] Additionally, a dysregulation of the orexinergic system, characterized by higher CSF–orexin levels, has also been linked to REM sleep reduction in MCI patients.[66] Furthermore, our results highlight that REM sleep instability is related to amyloid accumulation in the precuneus, posterior cingulate, orbitofrontal cortex, and the insula, which are among the first to exhibit amyloid deposition in AD.[67] This finding complements our previous observations that changes in REM sleep microstructure were associated with amyloid deposition in frontal, cingulate, and posterior regions in a partially overlapping sample.[8] Taken together, these results point toward REM sleep impairment as a marker of pathological aging. Of note, one might have expected SWS to be altered in Aβ+ individuals, as SWS alterations are thought to impair Aβ clearance[68] and have been associated with early amyloid deposition.[11,69] In our study, however, we did not observe such associations, likely because the wearable device only provided information on sleep architecture and did not allow us to quantify microstructural features such as slow-wave activity. Our

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findings of REM sleep instability should therefore be viewed as complementary to this literature: both REM sleep disruption and alterations in slow-wave activity may represent early markers of AD pathology, a possibility that needs to be clarified in future studies combining macro- and microstructural sleep measures.

Furthermore, neither TST nor REM sleep variability were associated with objective cognitive performance. This may reflect the fact that our sample comprised relatively highly educated older adults without cognitive deficits. Moreover, previous studies linking extreme sleep durations to cognitive impairment typically consider TST as a categorical factor, with both insufficient and excessive sleep being associated with impaired cognitive function.[70] Here, no participant showed abnormally long sleep duration (>9 hours), such that we analyzed TST as a continuous variable. Still, we found that longer TST was associated with greater subjective memory difficulties. As longer TST has been previously associated with dementia risk,[71] we cannot exclude that the observed association with greater subjective memory difficulties may reflect early signs of cognitive impairment, not yet objectified. Replication and longitudinal analyses are necessary to confirm this hypothesis. Of note, REM sleep alterations and irregular sleep patterns have also been associated with increased risk of cognitive decline and/or dementia.[12,25] Here, we did not observe any association between variability in REM sleep duration and cognitive performances. Tasks specifically designed to assess cognitive functions dependent on REM sleep, such as emotional memory processing, may better capture subtle cognitive changes associated with early REM sleep alterations.

In addition, we found no association between Aβ-related sleep metrics and psychoaffective outcomes (i.e., anxiety, depressive symptoms, and repetitive negative thinking), despite the fact that REM sleep is known to be involved in emotion regulation.[72] However, it should be noted that our sample excluded individuals with major psychiatric disorders, thereby reducing the range of psychoaffective symptoms severity. Chai et al.[17] proposed a model of temporal progression where sleep disturbances would precede Aβ accumulation, while anxious-depressive symptoms may appear later in AD progression. A complex interplay between these factors would subsequently lead to AD pathology accumulation, neurodegeneration, cognitive decline, and dementia. Despite potential interindividual variability in this temporal sequencing, we can hypothesize that anxious–depressive symptoms mostly emerge as a downstream consequence of greater sleep disturbances.

This study has several strengths, including the comprehensive phenotyping of participants for cognitive and behavioral symptoms, as well as amyloid burden. Additionally, the ecological assessment of sleep architecture at home over multiple nights is a novel approach in the field. To our knowledge, this is the first study to investigate night-to-night changes in sleep architecture in relation to early AD pathology. However, limitations include the limited number of recorded nights ($n = 4.5 \pm 0.8$) and the cross-sectional design preventing causal inference. Longitudinal studies are needed to determine whether Aβ-related sleep disturbances result from or contribute to amyloid accumulation over time. Although the Somno-Art device performs within the expected range for similar wearable devices, its ability to correctly classify sleep stages is a limitation that requires further replication. To our knowledge, this is the first study to investigate night-to-night variability in REM sleep duration in relation to amyloid accumulation. The prevalence-adjusted, bias-adjusted agreement between our device and PSG for REM sleep is substantial. Therefore, although our results are promising, they should be viewed with caution, and replication studies are warranted.

In conclusion, this study highlights the importance of considering both the mean and variability of sleep parameters when investigating the association between sleep quality and amyloid pathology in cognitively unimpaired individuals. Shorter sleep duration and greater variability in REM sleep duration appear as early markers of AD pathology and potential targets for interventions aimed at reducing AD risk and promoting healthy aging.

AUTHOR CONTRIBUTIONS

B.M. conceptualized the study, analyzed the data, and wrote the manuscript. G.R. and C.A. conceptualized the study, supervised the analysis, and wrote the manuscript. M.B., A.H., P.C., S.R., F.M., B.L., M.D., O.H., C.S., F.B., and G.C. contributed to data acquisition and analysis and reviewed the manuscript. The members of the Medit-Ageing Research Group and their respective contributions are detailed in the Appendix.

ACKNOWLEDGMENTS

The authors acknowledge all the participants of the study for their contribution. We are grateful to the PPRS company (Laurie Thiesse, Antoine Viola, René Gebel, Dylan Besson, and Baptiste Planat) for their support in Somno-Art data management, the Cyceron MRI-PET staff for neuroimaging data acquisition, as well as Aurélia Cognet, Valérie Lefranc, and Géraldine Poisnel for their administrative support. This work was performed on a facility of France Life Imaging network (grant ANR-11-INBS-0006). The Age-Well RCT is part of the Medit-Ageing project funded through the European Union's Horizon 2020 Research and Innovation Program (grant number 667696), Institut National de la Santé et de la Recherche Médicale (INSERM), Région Normandie, and Fondation d'entreprise MMA des Entrepreneurs du Futur. B.M. is funded by Fondation Perce-Neige. C.A. is funded by INSERM as part of the INSERM-FRQS Bilateral Collaborative Research Program on « Neurocognitive Aging ». Funding sources were not involved in the study design, data acquisition, analysis, interpretation, or manuscript writing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants gave written informed consent prior to the examinations.

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How to cite this article: Montagne B, Boulin M, Hamel A, et al. Night-to-night rapid eye movement sleep variability: A relevant marker of early amyloid-β deposition. *Alzheimer's Dement*. 2026;22:e71376. https://doi.org/10.1002/alz.71376

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APPENDIX: Collaborators – Medit-Ageing Research Group

Name	Affiliation/Location	Role	Contribution
Eider M. Arenaza-Urquijo, PhD	Institut National de la Santé et de la Recherche Médicale, Caen, France	Postdoctoral researcher	Study design; Acquisition, analysis, or interpretation of data
Florence Allais, BA	EUCLID/F-CRIN Clinical Trials Platform, Bordeaux, France	Data manager	Data management
Julien Asselineau, PhD	EUCLID/F-CRIN Clinical Trials Platform, Bordeaux, France	Statistician	Analysis of data
Sebastian Baez Lugo, MSc	University of Geneva, Geneva, Switzerland	PhD student	Acquisition, analysis, or interpretation of data
Alexandre Bejanin, PhD	Institut National de la Santé et de la Recherche Médicale, Caen, France	Postdoctoral researcher	Acquisition, analysis, or interpretation of data
Anne Chocat, MD	Institut National de la Santé et de la Recherche Médicale, Caen, France	Physician	Inclusion of participants
Fabienne Collette, PhD	University of Liege, Liege, Belgium	Group leader	Obtained funding; Study design
Sophie Dautricourt, MD, MSc	Institut National de la Santé et de la Recherche Médicale, Caen, France	PhD student	Acquisition, analysis, or interpretation of data
Eglantine Ferrand-Devouge, MD, MSc	Institut National de la Santé et de la Recherche Médicale, Caen, France	Physician	Inclusion of participants
Robin De Flores, PhD	Institut National de la Santé et de la Recherche Médicale, Caen, France	Postdoctoral Researcher	Acquisition, analysis, or interpretation of data; Administrative, technical, or material support
Hélène Esperou, MD	Institut National de la Santé et de la Recherche Médicale, Paris, France	Group leader	Sponsor
Eric Frison, MD	EUCLID/F-CRIN Clinical Trials Platform, Bordeaux, France	Methodologist	Study design; Interpretation of data
Julie Gonneaud, PhD	Institut National de la Santé et de la Recherche Médicale, Caen, France	Postdoctoral Researcher	Acquisition, analysis, or interpretation of data; Administrative, technical, or material support
Olga Klimecki, PhD	University of Geneva, Geneva, Switzerland	Neurologist	Obtained funding; Study design
Valérie Lefranc, BA	Institut National de la Santé et de la Recherche Médicale, Caen, France	Clinical research assistant	Acquisition, analysis, or interpretation of data; Administrative, technical, or material support
Antoine Lutz, PhD	Institut National de la Santé et de la Recherche Médicale, Lyon, France	Group leader	Obtained funding; Study design
Natalie Marchant, PhD	University College London, United Kingdom	Group leader	Obtained funding; Study design
Jose-Luis Molinuevo, MD, PhD	Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain	Group leader	Obtained funding; Study design
Léo Paly, MSc	Institut National de la Santé et de la Recherche Médicale, Caen, France	Neuropsychologist	Acquisition, analysis, or interpretation of data
Géraldine Poisnel, PhD	Institut National de la Santé et de la Recherche Médicale, Caen, France	Research engineer/Researcher	Obtained funding; Study design; Acquisition, analysis, or interpretation of data; Administrative, technical, or material support
Florence Requier, MSc	University of Liege, Liege, Belgium	PhD student	Acquisition, analysis, or interpretation of data
Eric Salmon, MD, PhD	University of Liege, Liege, Belgium	Group leader	Obtained funding; Study design
Siya Sherif, PhD	Institut National de la Santé et de la Recherche Médicale, Caen, France	Research engineer	Acquisition, analysis, or interpretation of data; Administrative, technical, or material support
Edelweiss Touron, PhD	Institut National de la Santé et de la Recherche Médicale, Caen, France	PhD student	Acquisition, analysis, or interpretation of data
Matthieu Vanhoutte, PhD	Institut National de la Santé et de la Recherche Médicale, Caen, France	Postdoctoral researcher	Acquisition, analysis, or interpretation of data; Administrative, technical, or material support
Patrik Vuilleumier, MD	University of Geneva, Geneva, Switzerland	Group leader	Obtained funding; Study design
Miranka Wirth, PhD	Deutsches Zentrum für Neurodegenerative Erkrankungen, Dresden, Germany	Group leader	Study design

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