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Sleep Characteristics and Cognition in Cerebral Amyloid Angiopathy: An Actigraphy-Based Study

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Abstract

This study investigated whether actigraphy-measured sleep characteristics are associated with cognition in patients with sporadic and Dutch-type hereditary cerebral amyloid angiopathy (CAA). CAA is characterized by amyloid-β deposition, increasing the risk of intracerebral hemorrhage and cognitive decline. As sleep is thought to support amyloid clearance, disruptions may exacerbate cognitive decline. We hypothesized that CAA patients would show disrupted sleep and cognitive impairments, with poorer sleep quality relating to worse cognitive performance.

Data came from two prospective cohorts at Leiden University Medical Center. Forty-eight participants (mean age = 62 years, 29% female) completed 14 nights of actigraphy and annual neuropsychological testing over five years. Sleep metrics (Total Sleep Time, Wake After Sleep Onset, awakenings, efficiency, fragmentation) were compared with normative values, while cognition (global, memory, speed, executive) was analyzed cross-sectionally and longitudinally. Sleep-cognition associations were examined using correlations and regressions with multiple-testing correction.

Compared to normative data, patients slept longer (median TST = 7.2 h vs. 6.3, $p < .001$) and showed higher sleep efficiency (86% vs. 78%, $p < .001$), but also more WASO (1.2 h vs. 0.9, $p < .001$) and more frequent awakenings (14.7 vs. 1.4, $p < .001$). Cognitive performance was largely preserved at baseline, with only a small proportion showing impairment (executive 14.6%, global 8.9%, memory 8.0%, speed 7.0%). Longitudinally, global cognition, speed, and executive function remained stable; memory showed a modest decline ($\beta = -0.107$ per year, $p = .005$), but this did not survive correction. No significant associations between sleep and cognition were observed cross-sectionally after adjustment.

These findings suggest that in CAA, sleep is characterized by fragmentation and increased nocturnal wakefulness, rather than reduced duration. Cognition was largely preserved with subtle vulnerabilities in memory and executive function. The absence of sleep-cognition associations at baseline may reflect preserved cognition, measurement limitations, and restricted sample size. Clinically, “poor sleep” in CAA may reflect altered sleep architecture rather than reduced sleep time. Scientifically, these results highlight the importance of focusing on qualitative sleep characteristics, particularly fragmentation and slow-wave activity, when studying sleep, vascular pathology, and cognition.

Layman's Abstract

Cerebral amyloid angiopathy (CAA) is a disease of the small blood vessels in the brain caused by deposits of a protein called amyloid-β. It increases the risk of brain bleeds and memory problems. Many patients also report poor sleep, and scientists believe sleep helps the brain clear away waste products such as amyloid-β. Because of this, sleep problems may play a role in worsening memory and thinking in CAA.

In this study, 48 people with CAA took part at Leiden University Medical Center. Their sleep was measured at home for two weeks with a wrist-worn device, and their memory and thinking were tested once a year for up to five years. We looked at how long they slept, how often they woke up at night, and how restful their sleep was.

We found that patients with CAA actually slept longer and spent more time in bed than people in the general population. Their sleep was also efficient overall. However, they woke up more often and spent more time awake after first falling asleep. This shows that their sleep was more restless, with many small interruptions.

When we looked at memory and thinking, most patients performed normally, with only small weaknesses in memory and executive skills (such as planning and problem solving). Over time, their scores remained fairly stable, with only slight signs of memory decline. Importantly, we found no clear link between sleep problems and thinking ability at the start of the study.

In summary, patients with CAA did not sleep less overall, but their sleep was more restless. Despite this, their memory and thinking remained relatively intact over time. This suggests that in CAA, "poor sleep" may mean restless, interrupted nights rather than fewer hours of sleep. Future studies should look more closely at the deeper stages of sleep, since these may play an important role in brain health. Understanding this connection could help doctors find new ways to protect memory and thinking in people with CAA.

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Introduction

Cerebral amyloid angiopathy (CAA) is a cerebral small vessel disease characterized by deposition of amyloid-β (Aβ) in the blood vessels of the brain's cortex and leptomeninges (Greenberg et al., 1993; Wermer & Greenberg, 2018). The accumulation of Aβ weakens the blood vessel walls, increasing the risk of lobar intracerebral hemorrhages and cerebral microbleeds (Viswanathan & Greenberg, 2011). Clinically, CAA is also associated with progressive cognitive decline, vascular dementia, and transient focal neurological episodes (van Etten et al., 2016; Wermer & Greenberg, 2018). CAA can be diagnosed during life using the Boston Criteria, which classifies cases as probable or possible CAA based on specific imaging markers and clinical data, whereas a definitive diagnosis requires post-mortem examination (Charidimou et al., 2022). The estimated prevalence of probable CAA is 5% to 7% in cognitively normal elderly individuals and 50% to 57% in those with lobar intracerebral hemorrhages (Jäkel et al., 2021).

While sporadic CAA (sCAA) is typically limited to the elderly population, Dutch-type hereditary CAA (D-CAA) has a significantly earlier age of onset and a markedly more progressive clinical disease course (Bornebroek et al., 1996; van Etten et al., 2016; Wermer & Greenberg, 2018). D-CAA results from a point mutation at codon 693 of the amyloid precursor protein gene, which leads to earlier and more extensive Aβ deposition compared to sCAA (Biffi, 2022). Most D-CAA patients clinically present with spontaneous intracerebral hemorrhage between the ages of 45 and 55, with approximately one-third not surviving their first occurrence (Biffi, 2022). D-CAA patients additionally have worse long-term prognosis after a first intracerebral hemorrhage than patients with sCAA (Gatti et al., 2020; van Etten et al., 2016). Despite these differences, sCAA and D-CAA share key clinical and pathological mechanisms underlying Aβ deposition. This makes D-CAA suitable for studying the early phases of the disease and a 'pure' form of CAA, without age-related comorbidities.

The glymphatic system is thought to be involved in clearing cerebral waste products such as Aβ (Inoue et al., 2021). One proposed pathway is via perivascular spaces, where cerebrospinal fluid moves through spaces surrounding the brain's arteries (perivascular spaces), enters the brain's network of small spaces between brain cells, and removes waste products via draining veins (Hablitz & Nedergaard, 2021; Inoue et al., 2021). Glymphatic function appears to follow a circadian, or 24-hour rhythm, where brain activity during slow-wave sleep correlates with increased glymphatic function, compared to diminished function during wakefulness or REM sleep (Hablitz et al., 2021). Rodent studies show that sleep enhances glymphatic activity, doubling Aβ removal compared to wakefulness (Rasmussen et al., 2018; Xie et al., 2013). Similar processes are believed to occur in humans, where actigraphy-measured fragmented 24-hour activity rhythms correlate with increased Aβ deposition (Nguyen et al., 2024), and even a single night of sleep deprivation is linked to elevated Aβ levels in key

brain regions (Shokri-Kojori et al., 2018). Disruptions in slow-wave sleep may further disrupt glymphatic function, possibly contributing to Aβ accumulation (Ju et al., 2017; Ooms et al., 2014). Poor sleep is therefore hypothesized to reduce glymphatic efficiency, potentially accelerating conditions such as CAA (Kozberg et al., 2020; Rasmussen et al., 2018). However, further research is needed to fully understand this connection.

Cognitive impairment is a clinical concern in the progression of CAA (van Dort et al., 2024). In D-CAA, cognitive impairment in memory and executive functions is evident, even in the early disease stages, whereas sCAA patients experience more pronounced deficits, particularly in memory and processing speed (van Dort et al., 2024; Xiong et al., 2016). These impairments are more evident in sCAA than in Alzheimer's Disease, mild cognitive impairment, or ischemic stroke (Case et al., 2016). Despite these differences in cognitive effects, the theoretical framework of studying CAA is heavily informed by Alzheimer's research, as both conditions share mechanisms underlying Aβ-related pathologies.

Aging is often accompanied by changes in sleep structure and quality, which can contribute to cognitive decline even in the absence of overt pathology (Cassagrande et al., 2022). Circadian rhythm disruptions are common among older adults but are more pronounced in individuals with neurodegenerative diseases, particularly Alzheimer's Disease (Leng et al., 2019). These disruptions often emerge early, preceding noticeable cognitive decline, and are thought to influence disease progression (Cordone et al., 2019). In Alzheimer's, sleep disturbances may manifest as increased nighttime activity, reduced daytime activity, and disruptions to the 24-hour rest-activity cycle (Leng et al., 2019). Compared to healthy older adults, Alzheimer's patients experience more frequent sleep interruptions, delayed bedtimes and wake times, and fragmented sleep-wake patterns marked by irregular sleep and daytime napping (Leng et al., 2019). These sleep disturbances can negatively impact cognitive functions (McCoy & Strecker, 2011). As cognitive impairment progresses, sleep disturbances tend to increase in frequency and severity (Cassagrande et al., 2022). Notably, Alzheimer's patients with less deep sleep tend to experience faster cognitive decline compared to those with more restorative sleep (Targa et al., 2021).

The sleep patterns observed in Alzheimer's Disease, such as shorter total sleep time, lower sleep efficiency, and increased wakefulness during the night, might suggest that similar sleep disturbances are present in patients with sCAA and D-CAA (Borges et al., 2021; Cordone et al., 2010). Existing studies have established a robust link between poor sleep quality and cognitive decline in Alzheimer's Disease, showing that poor sleep is associated with elevated Aβ burden and accelerated cognitive decline (Nguyen et al., 2024; Shokri-Kojori et al., 2018). However, studies on sleep disturbances in patients

with CAA are lacking. This gap in the literature highlights the need for further research to explore the impact of sleep disturbances on cognitive functioning in patients with CAA.

Therefore, the primary objective of this study was to investigate the association between actigraphy-measured sleep characteristics and cognitive performance in patients with CAA. Specifically, we aimed to determine whether cognitive performance, measured cross-sectionally and over time, was associated with sleep characteristics measured cross-sectionally. This study could provide valuable insights into the role of sleep in cognitive decline among patients with CAA, thereby enhancing our understanding of both the pathophysiological mechanisms and disease progression. Moreover, the findings may suggest that sleep represents a potential therapeutic target for mitigating cognitive decline or could serve as a clinical outcome measure in this population.

In addressing the association between actigraphy-measured sleep characteristics and cognitive performance in patients with CAA, we hypothesized that CAA patients would demonstrate shorter than average sleep duration, greater wakefulness during the night, and lower sleep efficiency. This expectation was based on existing evidence from conditions with similar Aβ-related pathologies, such as Alzheimer's Disease, where disrupted sleep patterns are commonly observed and may contribute to amyloid accumulation (Borges et al., 2021; Cordone et al., 2010). Clinical observations of CAA patients also frequently indicated poor sleep quality, further supporting this hypothesis. Furthermore, we expected to observe impairments in cognitive domains commonly affected in CAA, including executive functioning, processing speed, and memory (Arvanitakis et al., 2011; Xiong et al., 2016). These deficits were anticipated to be consistent with the impact of vascular pathology on brain function in this patient population. Lastly, we hypothesized that poorer sleep quality, characterized by shorter sleep duration, increased nighttime wakefulness, and reduced sleep efficiency, would correlate with worse performance in cognitive domains such as memory, attention, and executive functioning. This prediction aligned with prior evidence suggesting that disrupted sleep impairs glymphatic clearance of Aβ, potentially exacerbating cognitive decline (Greenberg et al., 2019; Ju et al., 2017). This hypothesis reflected the expected relationships between sleep quality, cognitive performance, and disease progression in the context of CAA.

Methods

Design

This study was a sub-project of the larger AURORA (D-CAA) and FOCAS (sCAA) studies conducted at the Leiden University Medical Center (LUMC), the Netherlands. These overarching studies have explored the natural history, disease progression, and biomarkers in sCAA and D-CAA populations from 2018 to 2024. For the current study, we employed a mixed-methods design, incorporating both

cross-sectional and longitudinal elements, to investigate the association between sleep patterns and cognitive performance in patients with sCAA and D-CAA (grouped). Data for this study included assessments of sleep quality measured via actigraphy and neuropsychological testing to evaluate cognitive performance and its potential decline over five years.

Participants

In this study, we included participants from two prospective cohorts: patients with sCAA from the sporadic CAA follow-up study (FOCAS; initiated in 2018) and patients with D-CAA from the hereditary CAA follow-up study (AURORA; initiated in 2018). Participants with sCAA were included if they were diagnosed with "probable CAA" based on the modified Boston Criteria 2.0 (Supplementary Table 1), which includes the presence of clinical symptoms of CAA (Charidimou et al., 2022). For D-CAA participants, the inclusion criteria required individuals to be aged 18 years or older and to have either a genetically confirmed amyloid precursor protein mutation or a medical history of one or more symptomatic or lobar intracerebral hemorrhages, alongside at least one first-degree relative with confirmed D-CAA. Participants who worked night shifts in the week before or during the measurement period, those at 50% genetic risk for D-CAA but without confirmed mutation, and those with non-compliant measurements (fewer than four consecutive days and nights of actigraphy measurements and filled out sleep diary) were excluded from the study.

Measures

We assessed cognitive performance using a standardized battery of validated neuropsychological assessments administered during annual visits. The cognitive domains most impacted by CAA are global cognition, memory, processing speed, and executive function (Schiavolin et al., 2024); accordingly, we selected cognitive assessments targeting each of these areas.

The Montreal Cognitive Assessment (MoCA) was used to evaluate global cognitive performance. This includes both short-and long-term memory, sustained and selective attention, executive function (including cognitive flexibility and inhibition), and language abilities (such as naming and verbal fluency). The MoCA has a score range of 0-30, where higher scores indicate better cognitive function. In accordance with the testing manual, scores of 25 or lower were considered indicative of cognitive impairment.

The Rey Auditory Verbal Learning Test - 15 words (RAVLT) was used to assess verbal learning and (short-and long-term) memory across three specific outcomes: immediate recall (sum of words recalled across learning trials), delayed recall (number of words remembered after a delay), and recognition memory (number of correctly identified words from a list). The scores we used are the

raw scores of the total number correct on trials 1-5 and the total number correct on delayed recall, where a higher score indicates better cognitive function.

The Stroop Color-Word Test (Stroop I, Stroop II, Stroop III) was used to assess cognitive flexibility, inhibition, and processing speed. Stroop I and II measure processing speed, while Stroop III evaluates inhibition. To isolate cognitive flexibility, the ratio of Stroop III (interference task) to Stroop II (congruent task) was calculated, controlling for processing speed. Higher ratios indicate greater difficulty in handling cognitive interference, which suggests poorer executive functioning. Longer completion time on any Stroop task indicates poorer performance.

Finally, the Trail Making Test (TMT-A, TMT-B) was used to assess executive functioning. TMT-A measures processing speed and visual attention, while TMT-B additionally evaluates cognitive flexibility. The TMT A and B are measured as time in seconds, where a higher completion time indicates lower cognitive function. Scores expressed as the TMT-B/TMT-A ratio are meant to assess cognitive flexibility while controlling for processing speed, where a higher ratio suggests poorer cognitive flexibility.

We assessed objective sleep quality with actigraphy measurements for 14 days (Kushida et al. 2001). Actigraphy data were recorded using GENEActiv accelerometers, worn around the non-dominant wrist continuously for 14 consecutive days and nights to monitor sleep and activity patterns, including total sleep time, sleep efficiency, and periods of wakefulness. The device was only removed during activities involving water, such as showering or swimming. Additional daily sleep diaries were used to assess subjective sleep-onset duration, as well as to monitor compliance and capture additional factors such as sleep medication use, caffeine intake, and reasons for sleep disturbances. Detailed information on the reliability and validity of the cognitive tests and actigraphy device is provided in Appendix 1.

Procedure

Demographic and medical history data, including age, sex, substance use (e.g., coffee, alcohol), and medical conditions (e.g., traumatic brain injury, hypercholesterolemia, hypertension, diabetes, migraine with aura, and depression), as well as clinical symptoms (e.g., history of intracerebral hemorrhage or transient focal neurological episodes), were collected during standardized annual visits. Trained researchers additionally administered a standardized neuropsychological assessment.

Based on the initial purpose of this paper, namely to ensure data compatibility between patients and controls, the collection of sleep-related data was designed to align with the methodology of the Rotterdam Study. Participants were given both written and verbal instructions and were asked to wear an Activinsights GENEActiv Original wrist-actigraphy watch for 14 days (measurement frequency 50Hz). Compliance was monitored through daily diaries, in which participants recorded their watch

usage and any relevant notes about their sleep. Secondary measures of mood and sleep quality were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), Hospital Anxiety and Depression Scale (HADS), and Pittsburgh Sleep Quality Index (PSQI). Upon completion of the 14-day monitoring period, participants returned the wrist-worn actigraphy devices by mail.

Ethical approval for the FOCAS (P17.259) and AURORA (P17.235) studies was obtained from the Medical Ethics Committee of Leiden Den Haag Delft. The current research project, titled "Sleep in CAA," was approved as an amendment within the FOCAS and AURORA studies by the METC of the Leiden University Medical Center in 2021. Written informed consent was obtained from all participants before their enrollment in the studies. Personal data were anonymized through the use of participant numbers, which were encrypted and securely stored in a protected database.

Statistical analyses

Preprocessing

All statistical analyses were performed in R (version 4.3.1) within RStudio using R Markdown. Before conducting the analyses, we pre-processed the actigraphy and sleep diary data to optimize sleep-wake scoring. We first cleaned the diaries following standard procedures from the Rotterdam Study (Dashti et al., 2016). We then processed the raw Geneactiv accelerometer files with the *GGIR* R package (van Hees et al., 2015) to extract nightly sleep parameters, incorporating the cleaned diary bed- and wake times to improve sleep detection. Combining objective actigraphy with subjective diaries is recommended because actigraphy alone may misclassify quiet wakefulness as sleep, while diaries help anchor the nocturnal sleep window and yield more valid estimates of sleep duration and efficiency (Ancoli-Israel et al., 2003; van Hees et al., 2018).

Sleep metrics and Normative Comparisons

Using this merged dataset, we then derived the sleep metrics of interest. Specifically, we derived total sleep time (TST), time in bed (TIB), wake after sleep onset (WASO), and the number of awakenings for each participant across up to 14 nights. From these, we computed sleep efficiency (SE = TST/TIB) and the sleep fragmentation index (SFI = awakenings/TST). Descriptive statistics were calculated to summarize the sleep characteristics in the original units, and raw values were converted to z-scores for comparison across measures. We quantified missingness by counting non-missing nights per variable and excluded any participant with fewer than four complete TST recordings. For each retained participant, we then summarized the sleep metrics using means and standard deviations.

To assess whether CAA patients' sleep metrics differed from normative expectations, we compiled reference values from large population-based actigraphy studies. Because no single study reported all metrics, we used multiple sources: van Hees et al. (2015) for Time in Bed and Total Sleep

Time (*N* = 4,094), Saint-Maurice et al. (2023) for awakenings ≥5 min (*N* = 40,943), Zijlmans et al. (2022) for WASO and Sleep Efficiency (*N* = 1,002), and Dashti et al. (2016) for the Sleep Fragmentation Index (*N* = 439). Patient averages were compared with these benchmarks using one-sample t tests or Wilcoxon signed-rank tests when normality was violated. All tests were two-sided with α = .05, and Bonferroni correction was applied to account for multiple comparisons.

Cognitive composites and Longitudinal Analyses

To examine cognitive performance in domains commonly impaired in CAA, we first defined cognitive domains following the method of Van Dort et al. (2024). Global cognition was defined through the MoCA; memory consisted of the RAVLT total score (trials 1-5) and delayed-recall score; processing speed was defined by the TMT-A, Stroop Condition I, and Stroop Condition II; and executive function was defined by both the TMT A/B ratio (cognitive flexibility) and the Stroop III／II ratio (interference time). Each raw score was converted into a z-score using the study sample means and standard deviations. Composite z-scores for each domain were calculated by averaging the relevant task z-scores. Descriptive statistics (mean ± *SD*, median [*IQR*], and proportion impaired) summarized performance, with cognitive dysfunction defined as a composite z-score ≤ -1 *SD* in all four domains (Van Dort et al, 2024).

To determine whether CAA patients differed from normative expectations, one-sample t-tests compared domain composite z-scores against a population mean of zero. Normality was assessed via Shapiro-Wilk tests and Q-Q plots. When normality assumptions were violated, the Wilcoxon signed-rank tests served as nonparametric alternatives. All tests were two-sided with α = 0.05, and a Bonferroni correction was applied for multiple domain comparisons. To evaluate cognitive change over time, we additionally fit linear mixed-effects models (random intercept per participant) with visit (factor) and, secondarily, time in months (continuous).

Sleep-cognition associations

Finally, to explore how sleep is related to cognition, we examined cross-sectional associations at baseline between key sleep parameters and domain-specific cognitive composites. Mean sleep metrics were each transformed into z-scores. We first assessed univariate normality of each sleep and cognitive variable via Shapiro-Wilk tests and Q-Q plots. For normally distributed pairs, Pearson's correlation was used; otherwise, Spearman's rank correlation was applied. Correlations were computed separately for each sleep measure and each cognitive domain composite (global cognition, memory, processing speed, executive function), with effect sizes reported as Pearson's *r* or Spearman's ρ (including 95 % confidence intervals for Pearson correlations). To control the false-discovery rate across multiple tests, p-values were adjusted using the Benjamini-Hochberg procedure.

In parallel, we fitted linear regression models predicting each cognitive composite from a composite SleepQuality index, constructed by averaging the z-scores of TST (reversed), SE (reversed), WASO, awakenings, and SFI. TST and SE were reversed so that higher values consistently reflected poorer sleep across all measures, ensuring comparability in the composite. Models were adjusted for baseline age and years of education. Regression coefficients (β), standard errors, t-statistics, and FDR-adjusted *p*-values were reported for the SleepQuality term in each model.

Results

Participants

Of 56 individuals who received actigraphy, 8 were excluded, yielding a final sample of 48 participants (see Supplementary Figure 1). Baseline demographic and clinical characteristics are summarized in Table 1. Overall, the cohort had a mean age of 62 years and was predominantly male. Most participants had completed middle to high education levels. Nearly half of the included participants had experienced a symptomatic intracerebral hemorrhage. Vascular risk factors (e.g., hypertension, high BMI), migraine with aura, neuropsychiatric symptoms (e.g., character changes, apathy, depression), and lifestyle factors (e.g., smoking, alcohol, coffee use) were common.

Table 1
Baseline characteristics

	All participants (*N*) **48**
Gender, *n (%)*	
Female	14 (29.2%)
Male	34 (70.8%)
Age Baseline, *mean (SD)*	62 (12.42)
Years of education, *mean (SD)*	14.2 (3.38)
Level of education*, *n (%)*	
Low	14 (29.2%)
Middle	18 (37.5%)
High	16 (33.3%)
Diagnosis, *n (%)*	
sCAA	30 (62.5%)
D-CAA	18 (37.5)
Symptomatic ICH*, *n (%)*	23 (47.9%)
Hypertension, *n (%)*	18 (37.5%)
Hypercholesterolemia, *n (%)*	15 (31.2%)
Diabetes Mellitus, *n (%)*	3 (6.2%)
High BMI*, *n (%)*	27 (56.2%)
Migraine with aura, *n (%)*	13 (27.1%)

Character changes, *n (%)*	30 (62.5%)
Apathy, *n (%)*	10 (20.8%)
Depression, *n (%)*	12 (25%)
Smoking, *n (%)*	
Never	12 (25%)
Former	33 (68.8%)
Current	3 (6.2%)
Alcohol use, *n (%)*	41 (85.4%)
Daily coffee use, *mean units (SD)*	3.29 *(3.07)*

Note. Education levels are categorized according to the Verhage (1965) scale: Low = primary education, lower vocational education, and lower secondary education. Middle = secondary vocational education and average-to-high secondary education. High = university of applied sciences or academic degrees. Symptomatic ICH is defined as an intracerebral haemorrhage accompanied by clinical symptoms. A body mass index (BMI) ≥ 25 kg/m² is considered high. Apathy, depression, and character changes are self-reported. Daily coffee consumption is expressed in the number of cups per day.

Sleep Characteristics

Descriptive Sleep Metrics

After excluding participants with fewer than four complete nights of recording, the remaining 47 participants contributed a median of 14 nights (range 12-15, mean = 12.98 nights). Participants spent on average more than 8 hours in bed, of which just over 7 hours were spent asleep. Total sleep time was not normally distributed. Wake after sleep onset was prolonged, with frequent awakenings. Despite this, sleep efficiency was relatively high, while the sleep fragmentation index indicated low levels of disruption. The full descriptive statistics for all sleep metrics are detailed in Table 2.

Table 2

Descriptive Sleep Metrics

Variable	*N*	Expected Mean (*SD*)*	*N*	Mean (*SD*)	*Median* (*IQR*)**
Total Sleep Time (TST, h)	4094	6.58 (0.94)	47	7.19 (1.65)	7.34 (6.67-7.80)
Time in Bed (TIB, h)	4094	7.6 (0.89)	47	8.43 (1.93)	NA
Wake After Sleep Onset (WASO, min)	1002	55.6 (23.3)	47	74.4 (46.8)	68.25 (58.56-88.26)
Number of Awakenings (count)	40 943	1.4 (NA)	47	14.67 (5.25)	NA

Sleep Efficiency (SE, %)	1002	77.6 (7.8)	47	86.0 (8)	NA
Sleep Fragmentation Index (SFI, awakenings/h)	439	6.1 (2.1)	47	2.04 (0.67)	NA

Note *Expected means are based on population means from the literature (van Hees et al., 2015; Dashti et al., 2016; Zijlmans et al., 2022; Saint-Maurice et al., 2023).**The median (IQR) is additionally calculated for the non-normally distributed metrics (TST and WASO).

Visual Inspection of Sleep across participants

The visual inspection of sleep metrics showed that participants generally spent around 7 hours asleep (TST range ~5-9 h) and 8.4 hours in bed, but WASO and awakening counts were right-skewed, with some nights exceeding 2 hours awake or 20 awakenings. Sleep efficiency remained high (>0.83) and fragmentation low (~2 awakenings/hour). These patterns mirror the summary statistics in Table 2 and explain our choice of nonparametric tests for TST and WASO. Supplementary Figure 2 shows the nightly distributions of our six sleep metrics.

Normality Assessment

Normality checks via Shapiro-Wilk tests (and confirmed by Q-Q plots) showed that mean TST ($W = 0.94$, $p = .027$) and mean WASO ($W = 0.89$, $p = .016$) violated the assumption of normality, whereas TIB ($W = 0.97$, $p = .090$), number of awakenings ($W = 0.99$, $p = .298$), sleep efficiency ($W = 0.97$, $p = .092$), and sleep fragmentation index ($W = 0.98$, $p = .193$) did not. Accordingly, we applied two-sided Wilcoxon signed-rank tests for TST and WASO, and one-sample t-tests for TIB, awakenings, SE, and SFI, each compared against its published normative mean (Table 3).

Statistical Comparisons to Normative Values

As summarized in Table 3, participants had significantly longer total sleep time and time in bed compared to normative values. Participants also showed higher sleep efficiency, but at the same time markedly elevated wake after sleep onset and a much greater number of nocturnal awakenings. In contrast, the sleep fragmentation index was significantly lower than the expected mean. All comparisons remained significant after Bonferroni correction.

Table 3
Sleep metrics and comparison to Normative Values

Variable	Normative mean (*SD*)	Sample Mean *(SD)*	Median	95% *CI*	*ES*	*Test statistic (df/V)**	*p-value*	*Adjusted p- value*
TST (h)	6.27 (0.85)	7.20 (0.95)	7.24	[6.98, 7.53]	*r*=0.72	*V*=1 030	8.39×10^{-7}	*p* < .001
TIB (h)	7.60	8.43 (1.01)		[8.13, 8.72]	*g*= 0.82 (0.81)	*t*(46) = 5.63	1.029×10^{-6}	*p* < .001
WASO (h)	0.93 (0.39)	1.23 (0.44)	1.14	[1.08, 1.31]	*r*= 0.63	*V*=973	1.54×10^{-5}	*p* < .001
Awakenings (count)	1.4	14.66 (3.54)		[13.62, 15.70]	*g*=3.74 (3.68)	*t*(46) = 25.67	$2.2 \times 10^{-}16$	*p* < .001
SE (%)	77.6 (7.8)	86 (5)		[84.3, 87.1]	*g*= 1.67 (1.64)	*t*(46) = 11.44	4.73×10^{-15}	*p* < .001
SFI	6.10 (2.10)	2.06 (0.49)		[1.917, 2.204]	*g*= −8.27 (−8.14)	*t*(46) = -56.72	$2.2 \times 10^{-}16$	*p* < .001

Note. All tests compare the sample mean (or median for non-normal variables) against published normative means (van Hees et al., 2015; Dashti et al., 2016; Zijlmans et al., 2022; Saint-Maurice et al., 2023). TST and WASO used Wilcoxon signed-rank tests; all others used one-sample t-tests. P-values are Bonferroni-adjusted across the six tests. All *p*'s remain significant after Bonferroni correction (adjusted *p* < .001 for all). *N* = 47. Effect size (ES)s: *d* and Hedges' *g* for one-sample t tests; Wilcoxon *r* for signed-rank tests (computed as *Z*/√N after removing zero differences).

Cognition

Cognitive Data Completeness

After computing composite z-scores and flagging impairment, we assessed data completeness at baseline (Supplementary Table 2). Of the 47 participants with actigraphy data, 45 (95.7%) provided valid global cognition composites, 25 (53.2%) had complete memory composites, 43 (91.5%) had processing speed composites, and 41 (87.2%) had executive function composites. Only two participants were missing a global cognition composite, 22 were missing memory, four were missing processing speed, and six were missing executive function composites. Completeness at the subsequent follow-up visits was calculated in the same manner (Supplementary Table 2).

Descriptive Cognitive Performance and Impairment at Baseline

Baseline composite z-scores were centered around the normative mean across all domains (Table 4). On the MoCA, most participants scored within the expected range, with a minority meeting the

impairment threshold. Memory performance, assessed with immediate and delayed recall on the RAVLT, was generally within the normative range, with few cases of impairment. Processing speed was close to the normative mean at the group level, although variability was observed across individual tasks (TMTA, Stroop I-II), and some participants met the impairment criterion. Executive function showed the highest proportion of impairment, with several participants performing below threshold on the TMT B and Stroop III despite mean scores being near the normative mean. Overall, impairment was most frequent in executive function, followed by global cognition, memory, and processing speed.

Table 4

Descriptive Cognitive Profile at Baseline (BL; *N* = 47)

Measure	**Value**
Global cognition	
Global cognition z-score, *mean* (*SD*)	0.00 (1.00)
MoCA, median (IQR)	27 (24.8-28)
MoCA impaired ($z \leq -1$), *n* (%)	4 (9.1%)
Memory	
Memory z-score, mean (*SD*)	0.00 (0.89)
RAVLT immediate recall, median (IQR)	28 (25-37)
RAVLT delayed recall, median (IQR)	6 (3-7)
Memory impaired ($z \leq -1$), *n* (%)	2 (8.0%)
Processing speed	
Processing speed z-score, mean (*SD*)	-0.02 (1.01)
TMTA, median (IQR)	31.5 (25-43)
Stroop I, s, median (IQR)	53 (45-62.25)
Stroop II, s, median (IQR)	71.5 (56.8-81.5)
Processing speed impaired ($z \leq -1$), *n* (%)	3 (7.1%)
Executive function	
Executive function z-score, mean (*SD*)	0.03 (0.85)
TMT Ratio (B/A), mean (*SD*)	2.61 (1.21)
TMT-B, s, median (IQR)	68.5 (52.8-110.3)
Stroop Ratio (III/II), mean (*SD*)	1.84 (0.47)

Stroop III, s, median (IQR)	120.5 (88.5-173.5)
Executive function impaired ($z \leq -1$), *n* (%)	5 (12.5%)

Note. Composite z scores are standardized within the study sample at each visit (so group mean ≈ 0, *SD* ≈ 1); raw times/scores are reported as median (IQR); impairment defined as composite $z \leq -1$. Abbreviations: MoCA, Montreal Cognitive Assessment; RAVLT, Rey-Auditory Verbal Learning Test; TMT, Trail Making Test; Stroop, Stroop Color-Word Test; IQR, interquartile range; SD, standard deviation.

Distribution of Baseline Cognitive Composites

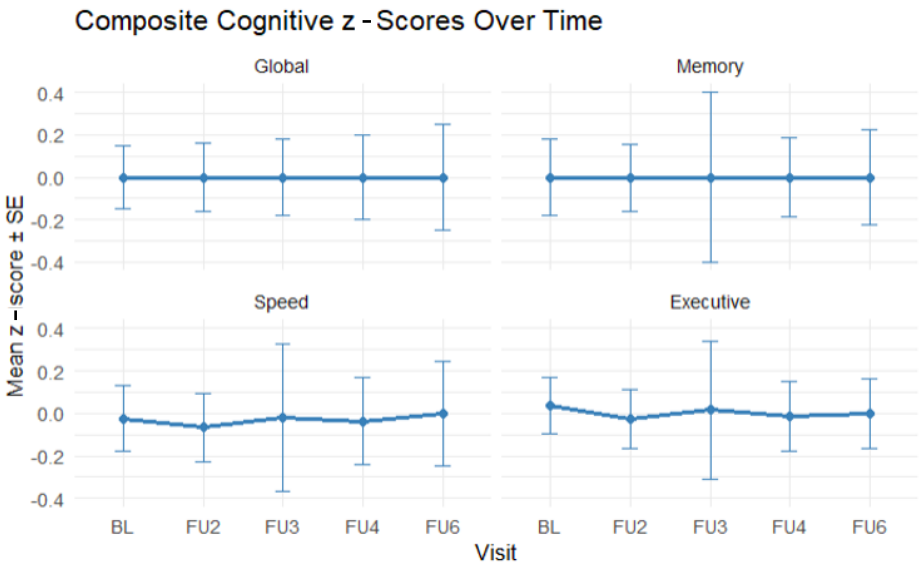
When additionally plotting each domain's distribution of baseline composite z-scores (Supplementary Figure 3), global cognition showed a tight distribution centered just above zero (median ≈ 0.1), with most participants between roughly -0.3 and +0.5 *z* and only one or two outliers dipping below -1. Executive function is similarly centered around zero (median ≈ 0.1) but with a slightly wider spread (IQR ≈ -0.3 to +0.4), again with a handful of participants below the impairment line. Processing speed also clusters just above zero (median ≈ 0.1), with relatively few values below -1 and one outlier up near +2 z. Memory stands out as shifted downward: its median is below zero (≈ -0.2), the lower quartile dips close to -0.6 *z*, and the whiskers extend further below -1, indicating more participants with memory performance in the impaired range. Overall, Global, Executive, and Speed composites are tightly distributed around the normative mean, whereas Memory shows both lower average performance and more scores crossing the clinical cutoff.

Cognitive Domain Trajectories Across Visits

Across the five study visits, mean composite z-scores in all four cognitive domains remained stable and close to the normative mean of zero (Figure 1). In the Global cognition and Executive function panels, the mean z-score at each visit hovers around 0.0, with relatively narrow ± *SE* bars (± ~0.15), indicating little drift or increased variability over time. The Processing Speed domain shows a slight dip at FU3 (mean ≈ -0.10), but quickly returns to near zero by FU4 and FU6; its error bars at FU3 are wider, reflecting greater between-participant variability at that time point. Memory exhibits the greatest fluctuation in variability: although the mean stays near zero, the *SE* at FU3 spans roughly -0.25 to + 0.35, suggesting that a subset of participants deviated more strongly from the group average on delayed recall at that visit. Overall, none of the domains demonstrate a systematic upward or downward trend, implying stable cognitive performance across the study period.

Figure 1

Trajectories of Composite Cognitive Z-Scores Across Visits



Note. Mean composite z scores (± SE) are shown for each visit. Composite scores are standardized to a normative mean of 0 (SD = 1). Sample sizes were n = 47 at BL, 42 at FU2, 35 at FU3, 26 at FU4, and 16 at FU6.

Comparison of Cognitive Composites to Normative Mean

Across all domains and visits (BL, FU2, FU3, FU4, FU6), one-sample tests of the composite z-scores against zero were not significant after Bonferroni or FDR correction (all adjusted $p \geq .47$), with estimates close to 0 and confidence intervals spanning 0 (Supplementary Table 3). For example, at baseline, Global cognition's median was 0.09 (Wilcoxon $V = 575$, $p = .35$), Memory's mean ≈ 0.00 ($t(24) = 0.00$, $p = 1.00$), Speed's median 0.11 (Wilcoxon $V = 540$, $p = .27$), and Executive's median 0.17 (Wilcoxon $V = 484$, $p = .32$). Because composites were standardized within the study sample at each visit, means are expected to be near zero; these tests are provided for completeness.

Normality checks

The visualization of the Normal Q-Q Plot of Residuals shows that, for all four cognitive domain models (Global cognition, Memory, Processing speed, Executive function), the vast majority of residuals fell along their reference lines, indicating that the assumption of normally distributed errors is reasonably met (Supplementary Figure 4). There is only a slight deviation at the extreme tails (a few points bending away at the very low end), which is common in small samples and not severe enough to invalidate the models. The Residuals vs Fitted Values plot displays residuals scattered randomly around zero across the full range of fitted values, with no discernible pattern or "fan-shaped" spread, indicating that the variance of the residuals is approximately constant (homoscedasticity). Taken together, these figures support the use of linear mixed-effects models for our longitudinal cognitive

data: residuals are acceptably normal and homoscedastic, so our inferences from the LME Visit effects (the omnibus F tests) are valid.

Additionally, the Shapiro-Wilk tests of baseline cognitive composites and raw scores revealed that several key measures deviated significantly from normality, indicating the need for nonparametric or robust modeling approaches for those metrics (Supplementary Table 4). Specifically, the memory composite (W = 0.928, p = .077) and both RAVLT immediate (W = 0.966, p = .555) and delayed recall (W = 0.957, p = .358), as well as the Stroop ratio (W = 0.919, p = .056), did not depart significantly from normality. In contrast, the global cognition, executive function, and processing speed composites, all MOCA scores, trail-making times and ratio, and the raw Stroop trial times showed highly significant non-normality (all p < .001), suggesting the use of Wilcoxon-type or robust mixed-effects methods for those variables. Accordingly, we used nonparametric summaries for memory, Stroop ratio, and RAVLT measures at baseline and applied robust or rank-based mixed-effects models for all other cognitive metrics.

Longitudinal Trajectories

Using linear mixed-effects models with a random intercept for each participant, we tested the fixed effect of Visit (BL, FU2, FU3, FU4, FU6) on the four composite domains (Table 5). Linear mixed-effects models with random intercepts per participant showed no significant omnibus Visit effects (longitudinal change) for any cognitive domain (all p > .09; Table 5). When examining linear trends over time, small but significant annual declines were observed in Global cognition (β = −0.075, p = .031) and Memory (β = −0.107, p = .005). Processing speed and Executive function showed no evidence of change across visits. Pairwise contrasts relative to baseline indicated lower Memory scores at FU4 and FU6, although these did not survive multiple-comparison correction. Per-visit sample sizes decreased at later follow-ups (e.g., FU3 N is as low as 6), reducing power and widening CIs.

Table 5

Linear mixed-effects models of cognitive domain composites: Visit contrasts vs baseline

Domain	**Contrast**	***N* (BL)**	***N* (Visit)**	**Estimate (B)**	***SE***	**95% *CI***	***P***	***P*(Bonf.)**	***q*(FDR)**
Global Cognition									
	FU2 vs BL	44	39	0.043	0.136	[-0.226, 0.312]	0.753	1.000	0.969
	FU3 vs BL	44	31	-0.006	0.146	[-0.296, 0.285]	0.969	1.000	0.969

	FU4 vs BL	44	25	-0.241	0.158	[-0.555, 0.072]	0.130	0.520	0.260
	FU6 vs BL	44	15	-0.359	0.192	[-0.741, 0.022]	0.064	0.258	0.258
	Slope/year	44		-0.075	0.034	[-0.142, -0.008]	0.031		
	Omnibus	44					0.173		
Memory	FU2 vs BL	25	33	-0.107	0.143	[-0.393, 0.180]	0.459	1.000	0.612
	FU3 vs BL	25	6	-0.051	0.259	[-0.570, 0.468]	0.844	1.000	0.844
	FU4 vs BL	25	24	-0.339	0.169	[-0.677, -0.000]	0.050	0.199	0.100
	FU6 vs BL	25	14	-0.51	0.207	[-0.925, -0.096]	0.017	0.067	0.067
	Slope/year	25		-0.107	0.037	[-0.181, -0.033]	0.005		
	Omnibus	25					0.091		
Processing Speed									
	FU2 vs BL	42	38	0.009	0.132	[-0.254, 0.272]	0.944	1.000	0.944
	FU3 vs BL	42	6	0.081	0.28	[-0.478, 0.639]	0.774	1.000	0.944
	FU4 vs BL	42	23	-0.077	0.158	[-0.392, 0.237]	0.624	1.000	0.944
	FU6 vs BL	42	12	-0.193	0.205	[-0.601, 0.215]	0.348	1.000	0.944
	Slope/year	42		-0.036	0.036	[-0.108, 0.036]	0.321		
	Omnibus	42					0.851		
Executive Function									

	FU2 vs BL	40	36	0.003	0.127	[-0.251, 0.257]	0.980	1.000	0.980
	FU3 vs BL	40	6	0.038	0.259	[-0.479, 0.554]	0.885	1.000	0.980
	FU4 vs BL	40	21	-0.015	0.153	[-0.321, 0.290]	0.920	1.000	0.980
	FU6 vs BL	40	12	-0.098	0.189	[-0.476, 0.280]	0.607	1.000	0.980
	Slope/year	40		-0.016	0.033	[-0.082, 0.050]	0.639		
	Omnibus	40					0.986		

Note. Estimates come from linear mixed-effects models with random intercepts per participant. Rows labeled "FUx vs BL" report the estimated difference (follow-up- baseline), where B is the fixed-effect estimate (negative = decline below baseline; positive = improvement). "Slope (per year)" reports the linear rate of change (β per year) since baseline. "Omnibus (Visit)" reports the overall F-test for a Visit effect. Confidence intervals are t-based using model degrees of freedom. *n* (BL) = number with baseline data in that domain; *n* (visit) = number contributing to that follow-up contrast. P-values for follow-up contrasts are adjusted within the domain using Bonferroni and Benjamini-Hochberg (FDR). B refers to the standardized regression coefficient.

Sleep and cognition at baseline

Normality checks

At baseline, total sleep time (TST) and sleep efficiency (SE) met the assumption of normality (Shapiro-Wilk $p > .10$), whereas wake after sleep onset (WASO), number of awakenings, and the sleep fragmentation index (SFI) did not (all $p < .001$). Among the cognitive composites, only memory and the Stroop ratio were normally distributed (both $p > .05$); all other composites (global, speed, executive) violated the normality assumption ($p < .001$). Accordingly, Pearson's r was used for TST, SE, memory, and Stroop ratio; Spearman's ρ for WASO, awakenings, SFI, and the remaining composites.

Zero-order correlations (SleepQuality index)

Using baseline composites, poorer sleep quality (higher SleepQuality index) showed no cross-sectional association with any cognitive domain after FDR correction (all FDR-adjusted $p = 0.863$). As summarized in Supplementary Table 5, domain-specific correlations were small and Cis all spanned zero, indicating no clear effect: Global cognition (Spearman ρ = −0.046, $n = 44$, 95% *CI* [−0.359, 0.269], $p = 0.765$), Memory (Pearson $r = -0.066$, $n = 25$, 95% *CI* [−0.450, 0.338], $p = 0.753$), Processing speed (Spearman ρ = −0.189, $n = 42$, 95% *CI* [−0.476, 0.152], $p = 0.232$), and Executive function (Spearman ρ = 0.028, $n = 40$, 95% *CI* [−0.312, 0.372], $p = 0.863$).

Covariate-adjusted regressions (SleepQuality index)

In age- and education-adjusted linear models, results were consistent: SleepQuality was not associated with Global cognition (β = −0.055, *SE* = 0.228, *t* = −0.24, *p* = .810, *FDR* = 1.000), Memory (β = −0.050, *SE* = 0.318, *t* = −0.16, *p* = .877, *FDR* = 1.000), or Executive function (β = 0.039, *SE* = 0.205, *t* = 0.19, *p* = .851, *FDR* = 1.000); for Processing speed the association was negative but not significant (β = −0.382, *SE* = 0.222, *t* = −1.72, *p* = .094, *FDR* = .378). Overall, adjusting for age and education did not change the bivariate conclusions: no cognitive domain showed a statistically reliable relationship with baseline SleepQuality after multiple-testing correction (Supplementary Table 6)

Zero-order correlations (individual sleep metrics)

We tested 20 zero-order correlations between sleep metrics (total sleep time, WASO, awakenings, sleep efficiency, sleep fragmentation) and cognitive composites (global cognition, memory, processing speed, executive function) (Supplementary Table 7). None of the associations survived Bonferroni or FDR correction (all adjusted *p* = 1.000). The largest uncorrected effect was observed between sleep efficiency and global cognition (*r* = .366, 95% *CI* [−.044, .670], *p* = .079), but this did not reach significance. Likewise, linear regression models predicting cognitive composites from our composite SleepQuality index (mean *z* of all sleep metrics), adjusted for age and education, yielded no significant effects after FDR correction (all adjusted *p* = 1.000). The strongest uncorrected trend was for processing speed (β = −0.382, *SE* = 0.222, *t* = −1.717, *p_raw* = .094, *p_fdr* = .378), but this also failed to survive correction. Although these results suggest that neither unadjusted correlations nor covariate-adjusted regressions provided support for cross-sectional sleep-cognition associations at baseline, it should be noted that the large number of tests may have obscured potential effects due to conservative correction.

Discussion

This study investigated whether actigraphy-measured sleep characteristics are associated with cognitive performance in patients with sporadic and Dutch-type hereditary CAA. Sleep is thought to support glymphatic clearance of amyloid-β (Ju et al., 2017; Nedergaard, 2020; Xie et al., 2013), while cognitive decline is a key clinical feature of CAA (van Dort et al., 2024; Xiong et al., 2016). Clarifying their association is therefore relevant both scientifically, by advancing understanding of disease mechanisms, and clinically, by identifying potential therapeutic targets and outcome measures.

Sleep Characteristics

We expected that patients with CAA would exhibit disrupted sleep patterns as measured by actigraphy. Specifically, we anticipated shorter sleep duration, greater wakefulness during the night,

and lower sleep efficiency compared to normative values (Dashti et al., 2016; Saint Maurice et al., 2023; van Hees et al., 2015; Zijlmans et al., 2022). Contrary to these expectations, patients with CAA slept longer on average and also spent more time in bed, indicating preserved or even extended sleep duration. In line with our prediction, however, they did show greater wakefulness after sleep onset and experienced a markedly higher number of awakenings during the night compared to normative data. Despite this, overall sleep efficiency was higher than expected, and the sleep fragmentation index was significantly lower, indicating that most time in bed was indeed spent asleep and that awakenings were likely generally brief. These findings seem to suggest that sleep in CAA is not globally impaired, but instead marked by preserved sleep quantity and efficiency alongside increased nocturnal wakefulness.

Notably, although patients showed a markedly higher number of awakenings, their sleep efficiency was paradoxically higher and their fragmentation index lower than normative values. This discrepancy likely reflects methodological differences in how awakenings and fragmentation are defined. Normative estimates for awakenings (Saint-Maurice et al., 2023) considered only events lasting ≥5 minutes, whereas actigraphy in our study classified many brief arousals as awakenings. Such micro-awakenings, while inflating the count, have limited impact on overall sleep duration or efficiency, thereby explaining the coexistence of frequent awakenings with preserved efficiency and reduced fragmentation compared to normative values (Fekedulegn et al., 2020).

Several explanations may account for the unexpected longer sleep duration and time in bed. First, the normative data used for comparison were derived from younger populations (van Hees et al., 2015), whereas our sample was significantly older. While aging is often associated with lighter and more fragmented sleep, actigraphy studies also report longer sleep duration in older adults (Li et al., 2018; Ohayon et al., 2004). This age effect, combined with the fact that longer sleep has been associated with cognitive impairment and dementia (Benito-León et al., 2009; Chen et al., 2016), may help explain the extended sleep observed in our cohort. Second, an extended sleep duration may reflect a compensatory response to underlying neural stress or dysfunction. In individuals at elevated risk for Alzheimer's disease, longer sleep duration has been observed up to 12 years before dementia onset, suggesting that increased time in bed may serve to preserve cognitive and metabolic resilience (Li et al., 2024). Third, comorbidities such as depression, alcohol use, hypertension, and hypercholesterolemia, which are common in our sample, may have contributed to longer time in bed, either through hypersomnia (Kaplan & Harvey, 2009; Nutt et al., 2008), disrupted sleep requiring compensatory rest (Ebrahim et al., 2013), or medication effects. For example, β-blockers are known to alter sleep architecture and increase fatigue, leading to extended time in bed (Stoschitzky et al., 1999; Tikhomirova et al., 2022).

The unexpectedly higher sleep efficiency may also reflect methodological and behavioral factors. Actigraphy relies on movement and often misclassifies periods of immobility as sleep, leading to overestimated efficiency in clinical populations who spend extended time in bed (Ancoli-Israel et al., 2015; Marino et al., 2013). Additionally, participants may compensate for fragmented sleep by remaining in bed longer, thereby increasing the likelihood of achieving sufficient total sleep. Such compensatory behavior has been documented in older adults and those with cognitive decline, and may inflate efficiency values without reflecting truly restorative sleep (Benito-León et al., 2009; Li et al., 2018). The lower sleep fragmentation index supports this interpretation, suggesting that although awakenings were frequent, they were typically brief and did not significantly disrupt overall continuity. Specifically, micro-awakenings can inflate measures of wake after sleep onset but may not meaningfully reduce the overall proportion of time spent asleep.

In contrast, the elevated wakefulness after sleep onset and the greater number of awakenings are in line with our expectations and with findings in related amyloid-β pathologies. For example, Alzheimer's disease patients experience frequent nocturnal awakenings and greater wakefulness than healthy controls (Leng et al., 2019), and similar clinical impressions exist for CAA. Importantly, such sleep disturbances may be mechanistically relevant. Increased nocturnal wakefulness likely reflects reduced restorative slow-wave sleep, which seems to be critical for glymphatic clearance of amyloid-β (Hablitz et al., 2021; Inoue et al., 2021; Xie et al., 2013). Disruption of this stage may impair clearance, thereby accelerating amyloid accumulation and disease progression (Ju et al., 2017; Kozberg et al., 2020; Ooms et al., 2014; Rasmussen et al., 2018). These findings underscore the importance of moving beyond sleep duration as the primary indicator of sleep quality. In CAA, "poor sleep" may manifest less as shortened sleep and more as altered architecture, characterized by micro-arousals and therewith diminished slow-wave sleep. Such qualitative disturbances may be particularly relevant for glymphatic dysfunction and disease progression, even when total sleep appears preserved.

Cognitive Functioning

We expected that patients with CAA would demonstrate impairments in cognitive domains commonly affected by vascular pathology, particularly executive functioning, processing speed, and memory (Arvanitakis et al., 2011; Xiong et al., 2016). Prior studies strongly support this expectation: CAA has been linked to widespread cognitive impairment, with executive dysfunction and slowed processing speed emerging as especially prominent deficits (Case et al., 2016; Xiong et al., 2016). More recent findings show that these difficulties can arise early in the disease course. For example, presymptomatic Dutch-type hereditary CAA carriers already perform worse on global cognition and executive function compared to controls (van Dort et al., 2024), and prospective data confirm that memory, processing speed, and executive functioning are the most vulnerable domains in sCAA (Theodorou et al., 2024).

This is consistent with broader literature on vascular cognitive impairment, where executive dysfunction and reduced processing speed are considered hallmark features (Moorhouse & Rockwood, 2008).

Contrary to these expectations, cognitive performance in our cohort was largely preserved. At baseline, average functioning across domains was close to normative values, though a subset of participants did show impairment. Executive function was most frequently affected, followed by global cognition, memory, and processing speed. Memory appeared slightly weaker overall, with a broader spread toward lower scores and a higher proportion of individuals crossing the impairment threshold compared to other domains. Longitudinally, cognitive trajectories remained relatively stable. Global cognition, processing speed, and executive function showed little evidence of systematic decline, while memory again appeared most vulnerable, with greater variability at follow-up and some participants performing below the group average. However, these changes were inconsistent and did not translate into a clear downward trend at the group level. Formal trajectory analyses revealed only small negative slopes for global cognition and memory, which did not survive correction for multiple comparisons.

Several factors may explain this relative preservation of cognition, despite expectations of decline. First, repeated neuropsychological testing is subject to practice effects, where prior exposure can artificially boost scores and obscure subtle declines in performance (Calamia et al., 2012). This is particularly relevant given that the same test battery was administered across multiple follow-ups. Second, although prior work in partly overlapping samples (van Dort et al., 2024) demonstrated early impairments in global cognition and executive function in presymptomatic D-CAA carriers, these effects were less evident in the present analyses. This discrepancy likely reflects methodological and design differences. Van Dort et al. compared carriers to matched controls (*N* = 159), allowing subtle group-level differences to emerge, whereas our study relied on normative reference values and within-group analyses, with a substantially smaller sample size. Moreover, pooling sCAA and D-CAA patients widened the distribution of age and disease severity: sCAA patients tend to be older and further along clinically, whereas D-CAA includes younger, sometimes presymptomatic carriers, in whom measurable decline is limited and emerges only gradually (van Dort et al., 2024). This heterogeneity likely inflated variance and attenuated detectable group differences relative to literature norms (van Etten et al., 2016), contributing to the absence of clear deviations from normative values in our study. Third, selective attrition likely biased our results: fewer participants completed later follow-ups, and those with greater impairment may have been less likely to return, leading later waves to overrepresent relatively healthier individuals (Case et al., 2016; Xiong et al., 2016).

Taken together, these explanations may account for the discrepancy between our findings and earlier reports of more pronounced cognitive impairment in CAA. They underscore the methodological challenges of detecting subtle cognitive decline in this population and highlight the need for sensitive measures, careful consideration of disease stage, and strategies to minimize attrition in future longitudinal research.

Sleep and Cognition

Finally, we hypothesized that poorer sleep quality, characterized by shorter sleep duration, increased nighttime wakefulness, and reduced sleep efficiency, would be associated with worse performance in cognitive domains such as memory, attention, and executive functioning. This expectation was grounded in extensive literature showing that disrupted sleep impairs glymphatic clearance of amyloid-β, a process believed to accelerate cognitive decline (Greenberg et al., 2019; Ju et al., 2017; Nedergaard, 2020). Poor sleep has consistently been linked to deficits in memory consolidation, attention, and executive processing (McCoy & Strecker, 2011; Rana et al., 2018). In Alzheimer's disease, reduced slow-wave sleep predicts faster cognitive decline (Targa et al., 2021), while actigraphy and polysomnography studies report shorter sleep duration, reduced efficiency, and greater nocturnal wakefulness (Borges et al., 2021; Cordone et al., 2010). Moreover, poor sleep quality has been tied to increased amyloid-β burden and accelerated cognitive decline (Nguyen et al., 2024; Shokri-Kojori et al., 2018), and population studies confirm associations between short sleep duration and impaired executive functioning in older adults (Tai et al., 2022; Winer et al., 2021). Based on this convergence of evidence, we expected similar relationships in CAA, where sleep disturbances would correspond to poorer cognitive outcomes.

Contrary to these expectations, baseline analyses revealed no significant associations between sleep quality and cognitive performance in any domain. Neither the composite sleep index nor individual sleep metrics predicted global cognition, memory, processing speed, or executive function. Although weak, non-significant trends suggested that poorer sleep might be related to slower processing speed and lower global cognition, these findings did not survive correction for multiple comparisons. Overall, sleep disturbances in this cohort did not correspond to measurable differences in cognitive function at baseline.

Several factors may explain this lack of association. First, cognitive functioning in the cohort was relatively preserved, with most participants scoring near normative levels and only a small subset showing impairment. When cognitive performance is intact, variability is restricted and ceiling effects limit sensitivity to subtle relationships (Salthouse, 2010). Second, the small sample size and selective attrition may have reduced power, particularly for memory composites, and biased results if more impaired individuals were less likely to complete assessments (Little et al., 2012). Finally, actigraphy

cannot capture sleep architecture such as slow-wave sleep, which is particularly relevant for glymphatic clearance and memory processes (Mander et al., 2017; Scullin & Bliwise, 2015), suggesting that meaningful associations may exist at the level of sleep stages rather than overall duration or efficiency.

Taken together, these explanations suggest that the absence of baseline sleep-cognition associations in this study does not necessarily contradict prior evidence. Instead, it underscores the importance of considering disease stage, measurement sensitivity, and study design in investigating this relationship. Future longitudinal and polysomnography-based studies will be essential to determine whether sleep disturbances contribute to cognitive decline in CAA over time.

Methodological Considerations, Future Directions, and Implications

A key strength of this study is its combination of actigraphy with a comprehensive cognitive test battery in a relatively rare patient population. The longitudinal design, with repeated measures over multiple years, allowed us to explore both cross-sectional and prospective associations between sleep and cognition. Additionally, including both sporadic and hereditary CAA cohorts provided a broader view of disease stages and trajectories, enhancing generalizability.

However, several limitations should be noted. First, attrition substantially reduced the sample size over time, with only 16 participants at the final follow-up, limiting power and potentially biasing results if more impaired individuals were less likely to return. Second, normative comparisons were based on heterogeneous published population data rather than matched healthy controls. Originally, the intention was to compare with age- and sex-matched controls from the Rotterdam Study, but due to data access limitations, this was not possible. The use of general normative values may have introduced discrepancies, especially given age differences between our sample and reference populations. Third, actigraphy provided valid, long-term sleep data but lacks sensitivity to sleep stages, overestimates sleep efficiency, and may miss alterations in slow-wave sleep, which is likely central to glymphatic clearance. Fourth, in cognition, ceiling and floor effects in some composites may have reduced sensitivity to subtle decline. Finally, while multiple-testing corrections minimized false positives, they also increased the chance of false negatives in this small sample.

Future research should focus on larger, multicenter cohorts with direct comparisons to age- and sex-matched controls, and would benefit from stratifying by CAA subtype or including subtype × age interactions to better isolate subtype-specific patterns. Combining actigraphy with polysomnography or EEG-based measures of slow-wave sleep would better capture the aspects of sleep most relevant to CAA. More frequent assessments across longer intervals, ideally linked with imaging and biomarker data, are needed to test whether sleep disturbances precede or accelerate cognitive decline.

Despite these limitations, this study provides a first systematic actigraphy-based characterization of sleep in CAA. The findings suggest that sleep in CAA is not globally impaired in terms of duration or efficiency but is characterized by fragmentation and increased nocturnal wakefulness. Cognitive functioning remained relatively preserved over time, with only subtle vulnerabilities in memory and executive function and no strong evidence of progressive decline during follow-up. Importantly, no cross-sectional associations between sleep and cognition were observed, suggesting that the relationship may only become evident at later disease stages or when more sensitive measures of sleep and cognition are used. Clinically, this suggests that subjective complaints of “poor sleep” in CAA may reflect alterations in sleep architecture rather than reduced total sleep time, with implications for how sleep disturbances are assessed and managed in this population. From a scientific perspective, our results emphasize the importance of moving beyond measures of sleep quantity and focusing on qualitative aspects of sleep, such as fragmentation and slow-wave activity, when investigating the interplay between sleep, vascular pathology, and cognition. Ultimately, a better understanding of these mechanisms may help identify sleep as a potential therapeutic target in CAA.

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Appendix 1: Psychometric properties of assessments

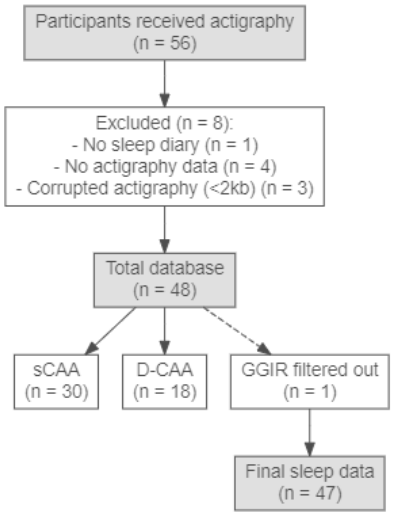
This appendix provides an overview of the reliability and validity of the cognitive assessments and actigraphy device applied in the present study.

The MoCA is a tool particularly sensitive to detecting mild cognitive impairment, with high reliability (Cronbach's alpha = 0.83) and established convergent validity with other global cognitive measures (Nasreddine et al., 2005). The RAVLT demonstrates high test-retest reliability (r = 0.80) and validity in measuring episodic memory (Vakil & Blachstein, 1997). The Stroop test is considered reliable (test-retest reliability > 0.70) and valid for assessing executive function and selective attention (Strauss et al., 2006). The TMT has strong reliability (r > 0.80) and established validity for assessing attention and executive function (Reitan, 1958). Finally, the GENEActiv device is a validated tool for measuring sleep patterns and has been shown to provide reliable data on sleep behavior in both healthy and clinical populations (Wullems et al., 2024).

Appendix 2: Supplementary Figures

Supplementary Figure 1

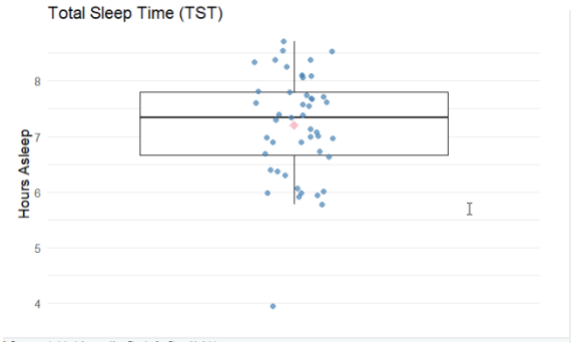
Flowchart of included participants

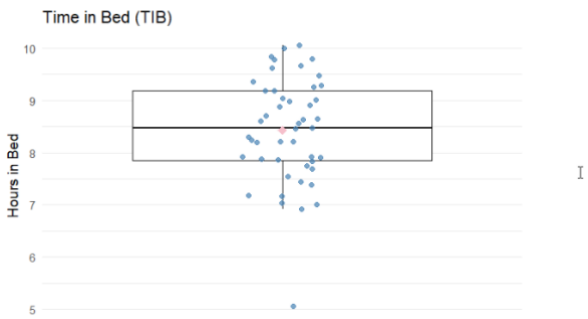


Note. Of 56 participants who received actigraphy, 8 were excluded due to missing sleep diary (*n* = 1), absent actigraphy data (*n* = 4), or corrupted recordings (< 2 kB; *n* = 3). One additional D-CAA participant's data were removed after GGIR quality filtering, leaving 47 participants with complete actigraphy sleep data.

Supplementary Figure 2

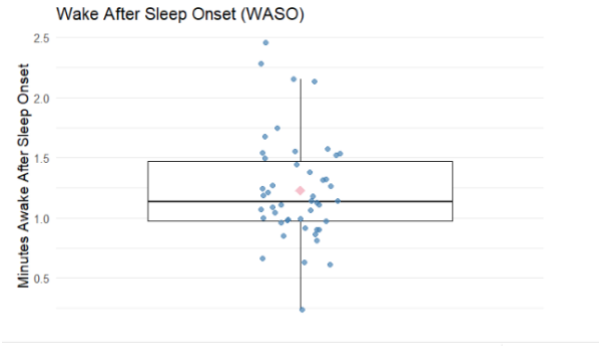
Visual inspection (boxplots) of all 6 sleep metrics' distribution across nights

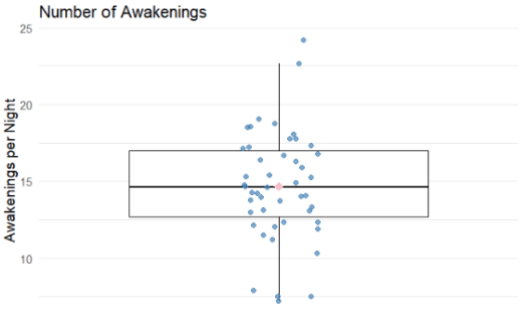




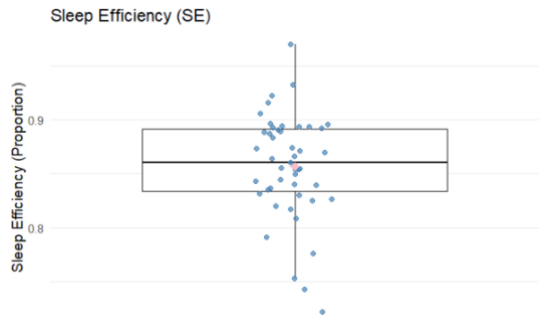
2A. Total Sleep Time (TST)

2B. Time in Bed (TIB)

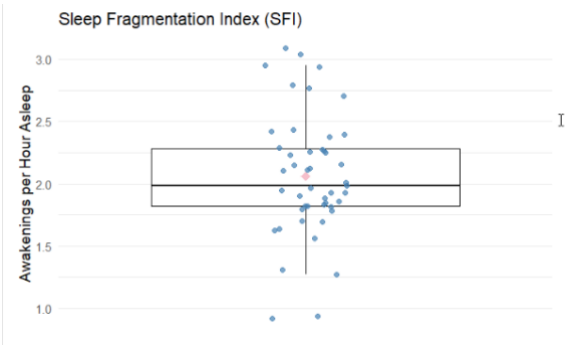




2C. Wake After Sleep Onset (WASO)



2D. Number of Awakenings



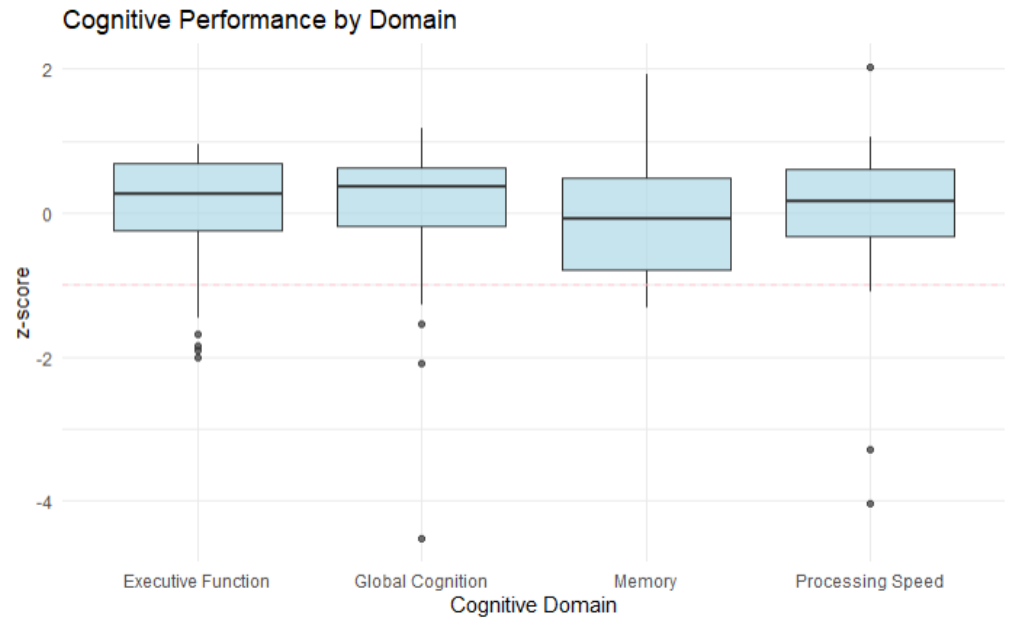
2E. Sleep Efficiency (SE)

2F. Sleep Fragmentation Index (SFI)

Note. Each panel shows a boxplot (median, IQR, whiskers to 1.5×IQR), overlaid individual points, and the group mean.

Supplementary Figure 3

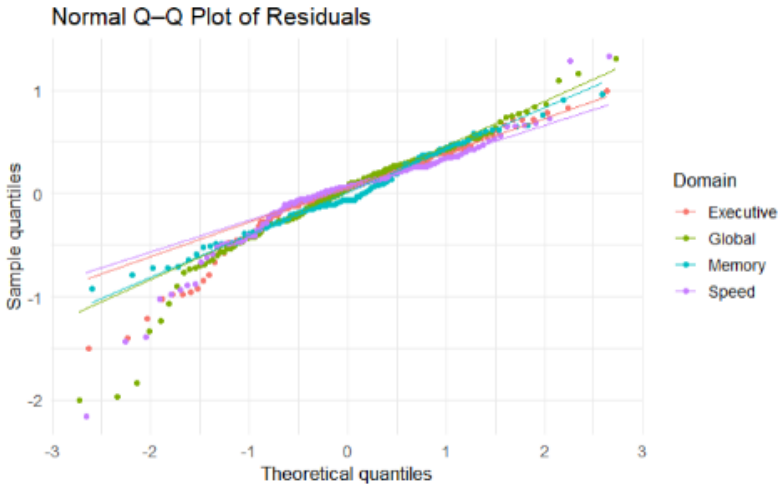
Baseline Cognitive Domain Boxplots



Note. Boxplots of baseline composite z-scores by cognitive domain. Boxes show the median and interquartile range (IQR); whiskers extend to 1.5 × IQR; dots are individual participants. The dashed red line marks the impairment cutoff at *z* = -1.

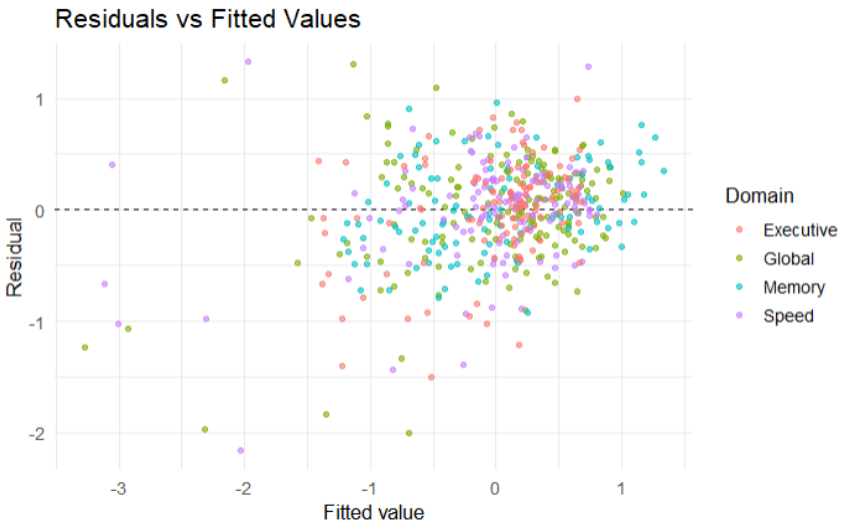
Supplementary Figure 4A

Normality check using Q-Q plot of residuals



Supplementary Figure 4B

Normality check plot Residuals vs. Fitted values



Appendix 3: Supplementary Tables

Supplementary Table 1

Modified Boston criteria for sCAA patients (Charidimou et al., 2022)

Panel: Boston criteria version 2.0 for sporadic cerebral amyloid angiopathy

1. Definite CAA

Full brain post-mortem examination demonstrating:

- Spontaneous intracerebral haemorrhage, transient focal neurological episodes, convexity subarachnoid haemorrhage, or cognitive impairment or dementia
- Severe CAA with vasculopathy
- Absence of other diagnostic lesion

2. Probable CAA with supporting pathology

Clinical data and pathological tissue (evacuated haematoma or cortical biopsy) demonstrating:

- Presentation with spontaneous intracerebral haemorrhage, transient focal neurological episodes, convexity subarachnoid haemorrhage, or cognitive impairment or dementia
- Some degree of CAA in specimen
- Absence of other diagnostic lesion

3. Probable CAA

For patients aged 50 years and older, clinical data and MRI demonstrating:

- Presentation with spontaneous intracerebral haemorrhage, transient focal neurological episodes, or cognitive impairment or dementia
- At least two of the following strictly lobar haemorrhagic lesions on T2*-weighted MRI, in any combination: intracerebral haemorrhage, cerebral microbleeds, or foci of cortical superficial siderosis or convexity subarachnoid haemorrhage

OR

- One lobar haemorrhagic lesion plus one white matter feature (severe perivascular spaces in the centrum semiovale or white matter hyperintensities in a multispot pattern)†
- Absence of any deep haemorrhagic lesions (ie, intracerebral haemorrhage or cerebral microbleeds) on T2*-weighted MRI
- Absence of other cause of haemorrhagic lesions‡
- Haemorrhagic lesion in cerebellum not counted as either lobar or deep haemorrhagic lesion

4. Possible CAA

For patients aged 50 years and older, clinical data and MRI demonstrating:

- Presentation with spontaneous intracerebral haemorrhage, transient focal neurological episodes, or cognitive impairment or dementia
- Absence of other cause of haemorrhage‡
- One strictly lobar haemorrhagic lesion on T2*-weighted MRI: intracerebral haemorrhage, cerebral microbleeds, or foci of cortical superficial siderosis or convexity subarachnoid haemorrhage

OR

- One white matter feature (severe visible perivascular spaces in the centrum semiovale or white matter hyperintensities in a multispot pattern)†
- Absence of any deep haemorrhagic lesions (ie, intracerebral haemorrhage or cerebral microbleeds) on T2*-weighted MRI
- Absence of other cause of haemorrhagic lesions‡
- Haemorrhagic lesion in cerebellum not counted as either lobar or deep haemorrhagic lesion

CAA=cerebral amyloid angiopathy. †Notable changes from the Boston criteria v1.5. ‡Other causes of haemorrhagic lesion: antecedent head trauma, haemorrhagic transformation of an ischaemic stroke, arteriovenous malformation, haemorrhagic tumour, CNS vasculitis. Other causes of cortical superficial siderosis and acute convexity subarachnoid haemorrhage should also be excluded.

Supplementary Table 2

Cognitive Data Completeness Across Visits (*N* = 47 at BL)

Cognitive Domain	BL *n* (valid) %	FU2 *n* (valid) %	FU3 *n* (valid) %	FU4 *n* (valid) %	FU6 *n* (valid) %
Global cognition	45 (95.7%)	40 (95.2%)	31 (88.6%)	26 (100%)	16 (100%)
Memory	25 (53.2%)	34 (81.0%)	6 (17.1%)	25 (96.2%)	15 (93.8%)
Processing speed	43 (91.5%)	39 (92.9%)	6 (17.1%)	24 (92.3%)	13 (81.3%)
Executive function	41 (87.2%)	37 (88.1%)	6 (17.1%)	22 (84.6%)	13 (81.3%)

Note. Percentages are calculated relative to *n*= 47 at BL, *n*=45 at FU2, *n*=35 at FU3 , *n*=26 at FU4 , and *n*= 16 at FU6

Supplementary Table 3

One-sample tests of cognitive domain composite z-scores against normative mean (0) at each study visit.

Visit	Domain	Test	*n*	Estimate (*z*)	95% *CI*	Test statistic	*p-value*	*p* (Bonf)	*p* (FDR)
BL	Global	Wilcoxon	44	0.091	[-0.176, 0.359]	*V* = 575	0.352	1.000	0.470
BL	Memory	t-test	25	0.000	[-0.369, 0.369]	*t(*24) = 0.00	1.000	1.000	1.000
BL	Speed	Wilcoxon	42	0.108	[-0.127, 0.315]	*V* = 540	0.271	1.000	0.470
BL	Executive	Wilcoxon	40	0.175	[-0.173, 0.411]	*V* = 484	0.323	1.000	0.470
FU2	Global	Wilcoxon	39	0.061	[-0.217, 0.339]	*V* = 455	0.367	1.000	0.570
FU2	Memory	t-test	32	-0.051	[-0.328, 0.321]	*t*(32) = -0.02	0.982	1.000	0.982
FU2	Speed	Wilcoxon	38	0.150	[-0.114, 0.326]	*V* = 455	0.223	0.893	0.570
FU2	Executive	Wilcoxon	36	0.089	[-0.105, 0.271]	*V* = 384	0.428	1.000	0.570
FU3	Global	Wilcoxon	31	0.172	[-0.178, 0.347]	*V* = 294	0.371	1.000	1.000
FU3	Memory	t-test	6	0.000	[-1.031, 1.031]	*t*(5) = 0.00	1.000	1.000	1.000
FU3	Speed	t-test	6	-0.021	[-0.915, 0.872]	*t*(5) = -0.06	0.953	1.000	1.000
FU3	Executive	t-test	6	0.017	[-0.818, 0.852]	*t*(5) = 0.05	0.961	1.000	1.000
FU4	Global	Wilcoxon	25	0.067	[-0.449, 0.583]	*V* = 184	0.571	1.000	0.835
FU4	Memory	t-test	24	0.000	[-0.393, 0.393]	*t*(23) = 0.00	1.000	1.000	1.000
FU4	Speed	Wilcoxon	23	0.189	[-0.201, 0.422]	*V* = 171	0.323	1.000	0.835
FU4	Executive	Wilcoxon	21	0.117	[-0.360, 0.409]	*V* = 130	0.627	1.000	0.835
FU6	Global	Wilcoxon	15	0.321	[-0.387, 0.462]	*V* = 85	0.163	0.652	0.652
FU6	Memory	t-test	14	0.000	[-0.492, 0.492]	*t*(13) = 0.00	1.000	1.000	1.000
FU6	Speed	t-test	12	0.000	[-0.571, 0.571]	*t*(11) = 0.00	1.000	1.000	1.000
FU6	Executive	t-test	12	0.000	[-0.374, 0.374]	*t*(11) = 0.00	1.000	1.000	1.000

Note. Estimate = mean (for t-test) or pseudomedian (for Wilcoxon). All tests were two-sided one-sample comparisons against 0. Bonferroni and FDR corrections applied across domains per visit.

Supplementary Table 4

Shapiro-Wilk Normality Tests for Baseline Cognitive Measures

Variable	*W*	*p*	Normality
Composite_Global_z_BL	0.7990	<.001	Non-normal
Composite_Memory_z_BL	0.9278	.0774	Normal
Composite_Executive_z_BL	0.8541	<.001	Non-normal
Composite_Speed_z_BL	0.7961	<.001	Non-normal
MOCA_BL	0.7990	<.001	Non-normal
RAVLT_Total_BL	0.9664	.5546	Normal
RAVLT_Delayed_BL	0.9570	.3575	Normal
TMTA_tijd_BL	0.8522	<.001	Non-normal
TMTB_tijd_BL	0.8670	<.001	Non-normal
TMT_Ratio_BL	0.8869	<.001	Non-normal
Stroop_1_tijd_BL	0.6911	<.001	Non-normal
Stroop_2_tijd_BL	0.7886	<.001	Non-normal
Stroop_Ratio_BL	0.9192	.0559	Normal

Note. Variables with $p < .05$ significantly deviate from a normal distribution according to Shapiro-Wilk, guiding the selection of appropriate statistical tests

Supplementary Table 5

SleepQuality-Cognition Correlations at Baseline

Domain	Method	*N*	Estimate (B)	95 % *CI*	*P*	*p* (FDR)
Global cognition	Spearman	44	-0.046	[-0.359, 0.269]	0.765	0.863
Memory	Pearson	25	-0.066	[-0.45, 0.338]	0.753	0.863
Processing speed	Spearman	42	-0.189	[-0.476, 0.152]	0.232	0.863
Executive function	Spearman	40	0.028	[-0.312, 0.372]	0.863	0.863

Supplementary Table 6

SleepQuality-Cognition Associations at Baseline (age- and education-adjusted linear models)

Domain	B	*SE*	*t*	*p*	*p* (FDR)
Global cognition	-0.055	0.228	-0.242	0.810	1.000

Memory	-0.050	0.318	-0.157	0.877	1.000
Processing speed	-0.382	0.222	-1.717	0.094	0.378
Executive function	0.039	0.205	0.189	0.851	1.000

Supplementary Table 7

Cross-Sectional Sleep-Cognition Correlations at Baseline (*N* = 47)

Mean Sleep Metric	Cognitive Composite	Method	Estimate (B)	95 % *CI*	*p*-value	*p*-bonf
TST	Global cognition	Pearson	0.009	(-0.395, 0.411)	0.965	1
TST	Memory	Pearson	0.249	(-0.171, 0.593)	0.240	1
TST	Processing speed	Spearman	-0.004	NA	0.984	1
TST	Executive function	Spearman	-0.117	NA	0.585	1
WASO	Global cognition	Spearman	-0.239	NA	0.260	1
WASO	Memory	Spearman	0.123	NA	0.567	1
WASO	Processing speed	Spearman	-0.199	NA	0.351	1
WASO	Executive function	Spearman	-0.079	NA	0.713	1
Awakenings	Global cognition	Pearson	0.122	(-0.296, 0.500)	0.571	1
Awakenings	Memory	Pearson	0.189	(-0.232, 0.550)	0.377	1
Awakenings	Processing speed	Spearman	0.107	NA	0.620	1
Awakenings	Executive function	Spearman	0.088	NA	0.682	1
SE	Global cognition	Pearson	0.366	(-0.044, 0.670)	0.079	1
SE	Memory	Pearson	0.123	(-0.295, 0.501)	0.568	1
SE	Processing speed	Spearman	0.113	NA	0.599	1
SE	Executive function	Spearman	0.017	NA	0.936	1
SFI	Global cognition	Pearson	0.099	(-0.317, 0.483)	0.644	1
SFI	Memory	Pearson	-0.045	(-0.441, 0.365)	0.834	1
SFI	Processing speed	Spearman	0.063	NA	0.771	1
SFI	Executive function	Spearman	0.183	NA	0.391	1

Note. Estimates are Pearson's *r* or Spearman's ρ as indicated; 95 % confidence intervals are shown for Pearson correlations only. All p-values were adjusted across the 20 tests using Bonferroni correction (p_bonf).

Appendix 4: Additional supplemental materials

Any additional supplemental materials, such as documentation of decision-making during data cleaning, R code used for preprocessing and analysis (including the running of GGIR), and further statistical analyses, may be made available upon request. Requests can be directed to y.alladin@lumc.nl. Sharing of these materials will only be possible after permission has been granted by the LUMC supervisors and when this can be done in an ethically responsible manner. Providing access to such materials is intended to contribute to transparency and to support open science practices.