Alzheimer's Research & Therapy

RESEARCH

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Self-reported sleep quality and longitudinal amyloid burden in clinically unimpaired adults from the AMYPAD PNHS study

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Abstract

Background Poor self-reported sleep quality is associated with cognitive impairment. Alzheimer's disease (AD) patients present sleep disruptions decades before they start to decline clinically. Similarly, amyloid-β (Aβ) starts accumulating during the preclinical phase of the disease. This study investigated associations between self-reported sleep quality and Aβ burden longitudinally in clinically unimpaired (CU) adults.

Methods Four hundred seventeen CU adults from the AMYPAD PNHS cohort were included, with baseline self-reported sleep quality assessments (Pittsburgh Sleep Quality Index, PSQI) and longitudinal Aβ PET scans. Participants were categorized by baseline Aβ levels as negative (A-), grey-zone (GZ), or positive (A+). Linear mixed-effects (LME) models tested the association between baseline sleep quality and Aβ burden over time, including interaction effects with baseline Aβ status.

Results Global PSQI score was not associated with Aβ burden over time in the entire group. However, a significant interaction with baseline Aβ status was found, whereby poorer subjective sleep quality was linked to accelerated Aβ accumulation in GZ participants.

Conclusions Poorer subjective sleep quality is associated with faster Aβ accumulation in CU individuals with intermediate Aβ levels, highlighting sleep as a potential target for early AD prevention and identifying an optimal intervention window.

Keywords Sleep, Amyloid PET, Alzheimer's disease; preclinical Alzheimer's disease

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Background

Amyloid-β (Aβ) plaque deposition in specific brain regions is a well-established pathological hallmark of Alzheimer's disease (AD) [1, 2]. Notably, Aβ accumulation can begin decades before the emergence of cognitive symptoms [3, 4], and sleep disturbances have also been described in this preclinical stage [5], suggesting a potential link between sleep and early AD pathology.

Sleep quality naturally deteriorates with age, with approximately half of the elderly population reporting difficulties initiating or maintaining sleep [6, 7]. Poor sleep quality has been consistently associated with reduced cognitive performance [8–13] and an increased risk of dementia [11, 14–16]. Moreover, sleep disturbances are highly prevalent among individuals with AD [17–22], often exacerbating caregiver burden and accelerating patient institutionalization [23]. Importantly, brain regions involved in regulating the sleep–wake cycle, such as the medial prefrontal cortex and the locus coeruleus, are affected early in the progression of AD [24–26].

Emerging evidence highlights a bidirectional relationship between sleep and Aβ dynamics [20]. Sleep and circadian rhythms drive daily fluctuations of soluble Aβ within the brain's interstitial fluid [27]. During wakefulness, neuronal activity promotes Aβ production, whereas during deep, slow-wave sleep, synchronized neuronal firing facilitates the clearance of neurotoxins, including Aβ, through the glymphatic system [28–30]. This clearance is supported by an increase in interstitial space volume, enhancing cerebrospinal fluid (CSF) and interstitial fluid exchange [31, 32].

Consequently, poor sleep quality is hypothesized to both increase Aβ production and impair its clearance, predicting a net accumulation of soluble Aβ within the brain's interstitial spaces [33, 34]. Prolonged or chronic sleep disruption may, therefore, accelerate the conversion of soluble Aβ into insoluble amyloid plaques, a process directly influenced by protein concentration levels. Furthermore, Aβ plaque deposition in sleep-regulating brain regions may, in turn, exacerbate sleep disturbances [5, 35, 36], creating a self-reinforcing feedback loop [20] that aggravates Aβ pathology. Given this intricate interplay, targeting sleep quality during the preclinical stage of AD emerges as a promising therapeutic strategy to slow down Aβ deposition. Additionally, monitoring sleep quality may serve as a non-invasive biomarker for tracking the progression of Aβ pathology.

Cross-sectional studies have linked worse self-reported sleep quality with a higher Aβ burden, as measured by CSF biomarkers [37–41] or with positron emission tomography (PET) scans [42–45] in cognitively normal adults. However, the longitudinal relationship between subjective sleep quality and Aβ accumulation remains unclear. One study [41] found that subjective sleep disturbances were linked to longitudinal changes towards more pathological CSF Aβ42 levels, but not tau, in a cohort of CU individuals. In contrast, a second study conducted in a smaller cohort of individuals [46], which included only 15 preclinical AD cases within a broader AD-spectrum group, found no association between longer subjective total sleep time and Aβ accumulation. Instead, longer subjective sleep duration was linked to greater tau accumulation, both cross-sectionally and longitudinally, based on PET imaging. These results underscore the need for further investigation into how self-reported sleep quality influences Aβ dynamics over time during the preclinical stage of AD.

In this study, we leveraged data from the pan-European multi-cohort Amyloid Imaging to Prevent Alzheimer's Disease – Prognostic and Natural History Study (AMYPAD PNHS) study [47, 48]. We aimed to explore whether baseline self-reported poor sleep quality is associated with greater Aβ burden over time in CU adults, using Aβ PET scans harmonized via the Centiloid scaling method [49]. Our findings may provide important insights into the role of sleep in the early progression of AD and inform future preventive strategies.

Methods

Design and participants

This is a prospective cohort study design including 417 CU adults – clinical dementia rating (CDR) score = 0 – from the AMYPAD PNHS cohort (https://doi.org/10.5281/zenodo.8017084) [48]. Participants were drawn from three parent cohorts – ALFA+, for ALzheimer and FAmilies [50], EPAD LCS, for European Prevention of Alzheimer's Dementia Longitudinal Cohort Study [51], and FACEHBI, for Fundació ACE Healthy Brain Initiative [52] – spanning 10 different countries. All participants completed a baseline visit that included assessments of self-reported sleep quality, mood evaluations, and quantification of baseline amyloid deposits in the brain (within less than 12 months), followed by at least one visit where amyloid deposition was measured again. All participants were CDR = 0 at baseline and were not discarded if converted to CDR > 0 in the subsequent visits.

Sleep assessment

Self-reported sleep quality was assessed at baseline using the global score of the Pittsburgh Sleep Quality Index (PSQI; [53]) in all the cohorts. The PSQI test is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month time interval. Questions included subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication use, and daytime dysfunction. The sum of the scores of these seven components yields the global PSQI score. Global scores range from 0 to 21, with higher scores reflecting worse sleep quality.

Amyloid burden quantification

To measure the Aβ burden, Aβ PET scans were acquired according to the standard protocol using either [^{18}F]florbetaben (Neuraceq®) or [^{18}F]flutemetamol (Vizamyl®) radiotracers and then quantified in Centiloid (CL) units with IXICO's pipeline, using the whole cerebellum as reference region [54]. All PET scans were processed using a fully automated workflow. All PET scans in the PNHS study were processed using a fully automated workflow [55]. For each subject, a CT scan was acquired for attenuation correction, followed by acquiring amyloid PET scans in four frames of 5-min. PET emission data were reconstructed using standardized, site-specific reconstruction protocols. To correct for head motion, individual PET frames were co-registered within each subject. All scans then underwent visual quality control to ensure the absence of significant motion artifacts. To reduce inter-scanner and inter-site variability, PET images were retrospectively harmonized using a post-reconstruction Gaussian smoothing filter, with kernel parameters defined separately for each site [56]. For Centiloid quantification, harmonized PET images were co-registered to the corresponding T1-weighted MRI scans. Cortical regions of interest (ROIs) were defined in native space by segmenting the T1-weighted MRI using the LEAP approach and subsequently reslicing these ROIs to match PET image resolution [57]. Standardized uptake value ratios (SUVRs) were then calculated using a cortical composite region that included frontal, temporal, and parietal cortices, as well as the precuneus, striatum, and insular cortex. The whole cerebellum was used as the reference region [58]. Finally, SUVR values were converted to Centiloid units using tracer-specific transformation equations derived in accordance with GAAIN methodological recommendations. No partial volume correction was applied to PET images. Participants were categorized into three groups based on baseline Aβ levels: negative (A-, CL < 12), grey-zone (GZ, 12–50 CL), and positive (A+, CL > 50) [59, 60]. Of the 417 participants included in the study, 336 participants (81%) had one follow-up visit at a mean of 2.8 years (SD 0.8, range 1.1–5.6) from baseline, and 81 participants (19%) had two follow-up visits that spanned an average of 5.3 years (SD 0.2, range 4.9–5.7).

Mood and anxiety assessment

A joint dichotomous variable indicating the presence of clinically relevant anxiety or depression symptoms was derived from the Hospital Anxiety and Depression Scales (HADS > 7) for the ALFA + and the FACEHBI cohorts, and from the Geriatric Depression Scale (GDS-30 > 9) and the State-Trait Anxiety Inventory (STAI > 59) for the EPAD LCS cohort, given that this cohort used separate instruments to assess depression and anxiety, respectively.

Statistical analysis

Group differences between baseline Aβ categories (A-, GZ, or A+) were tested using ANOVA or ANCOVA (controlling for age, sex and *APOE* status), followed by Tukey's Honestly Significant Difference (HSD) test to correct for multiple comparisons.

To explore the relationship between self-reported sleep quality and amyloid burden, linear mixed-effects (LME) models were employed. In these models, time (in years) was referred to the baseline PET visit. The small time difference between the sleep assessment and the PET scan in this baseline visit was reported in Table 1, but not considered in the models. The interaction term between PSQI global score and time, age at baseline, sex, presence of anxiety or depression, Apolipoprotein E (*APOE)*-ε4 status, and cohort were included as fixed effects. Random intercept and random slopes were included to capture the variability across subjects. Model 1 examined the effect of self-reported sleep quality (PSQI global score) on Aβ accumulation over time.

Table 1 Demographics and key variables across baseline amyloid PET categories

	Total (*n* = 417)	A- (*n* = 309, 74.1%)	GZ (*n* = 85, 20.4%)	A+ (*n* = 23, 5.5%)	*p* value
Age (years)—mean (SEM)	63.44 (0.31)	62.62 (0.37)	65.36 (0.62)	67.26 (1.07)	<0.001 **,[a]
Sex (females)—n (%)	252 (60.4)	187 (60.5)	50 (58.8)	15 (65.2)	0.855
APOE-ε4 (carriers)—n (%)	181 (43.4)	112 (36.2)	51 (60.0)	18 (78.3)	<0.001 **,[a]
Anxiety (yes)—n (%)	98 (23.5)	73 (23.6)	18 (21.2)	7 (30.4)	0.646[a]
Depression (yes)—n (%)	29 (7.0)	20 (6.5)	7 (8.2)	2 (8.7)	0.805[a]
Anxiety or Depression (yes)—n (%)	102 (24.5)	76 (24.6)	19 (22.4)	7 (30.4)	0.722[a]
PSQI (global score)—mean (SEM)	5.78 (0.17)	5.83 (0.21)	5.42 (0.35)	6.52 (0.72)	0.415[b]
PET baseline (CL)—mean (SEM)	9.09 (0.94)	0.41 (0.35)	24.63 (1.22)	68.41 (3.05)	<0.001 **,[b]
Time PSQI-PET (days)—mean (SEM)	71.15 (3.79)	69.91 (4.08)	82.07 (10.28)	47.52 (14.62)	0.055[b]
PET visits (number)—mean (SEM)	2.19 (0.02)	2.21 (0.02)	2.13 (0.04)	2.17 (0.08)	0.159[b]

A-: negative (CL < 12), GZ: grey-zone (12–50 CL), A+ : positive (CL > 50)

SEM Standard Error of the Mean, *APOE* Apolipoprotein E, *PSQI* Pittsburgh Sleep Quality Index

[a] *p* values correspond to ANOVA

[b] *p* values correspond to ANCOVA adjusted for age, sex and *APOE* status

** represents $p<0.001$ in both ANOVA [a] and in ANCOVA [b] analyses

Given the nonlinear trajectory of the rate of accumulation of Aβ (Guo et al., 2018), Model 2 included a three-way interaction term (time × subjective sleep quality × Aβ baseline category) to test the hypothesis that baseline Aβ status should modify the relationship between baseline PSQI scores and Aβ deposition over time. To facilitate interpretation of the interaction analyses, stratification analyses were conducted for each baseline Aβ category. In all analyses the global PSQI score was used as a continuous variable. However, to enhance the visual interpretability of the results, we depicted the predicted amyloid trajectories for three representative values of PSQI, corresponding to the median global PSQI score of each tertile (0 to ⅓, ⅓ to ⅔, and ⅔ to 1) using the whole sample: 3 for good, 6 for medium and 10 for poor sleep quality.

Sensitivity analyses were conducted to confirm the robustness of the results on the interaction model (Model 2) first by removing the participants of the A+ category (given the small sample size of it) and second by excluding participants with either anxiety or depression which are known to affect self-reported sleep quality.

Due to the small number of tests, and the fact that they were hypotheses driven, we did not correct for multiple comparisons in these analyses.

Analyses were performed using Python (version 3.9.18) and R (version 4.5.1). Statistical significance was considered at $p < 0.05$.

Results

Sample characteristics

The sample included 417 CU adults (mean age 63 years; 60% females; 43% *APOE*-ε4 carriers). Among them, 24.5% reported symptoms of anxiety (23.5%) and/or depression (7.0%). The average PSQI global score was 5.78 ± 0.17. The average time between the sleep assessment and the first PET visit was 71.15 ± 3.79 days. Based on the baseline Aβ PET scans, 309 participants were classified as A- (74%, mean CL = 0.41 ± 0.35), 85 as GZ (20%, mean CL = 24.63 ± 1.22), and 23 as A+ (6%, mean CL = 68.41 ± 3.05). Participants were classified as *APOE*-ε4 carriers if they carried either one or two ε4 alleles. There were significant group differences in terms of age and percentage of *APOE*-ε4 carriers: participants in the A- group were younger and had less APOE-ε4 carriers than in the other groups. The groups did not differ based on the presence of anxiety or depression, the PSQI global score, the time between first PET visit and the sleep assessment, or the number of follow-up visits (Table 1).

Females (Supplementary Table 1) and participants with anxiety or depression (Supplementary Table 2) reported significantly worse subjective sleep quality compared to males and participants without anxiety or depression. However, sex or the presence of anxiety or depression was not associated with differences in the levels of amyloid PET at baseline. On the contrary, *APOE*-ε4 carriers showed significantly higher values of PET at baseline without showing significant differences in subjective sleep quality compared to non-carriers (Supplementary Table 3). The ALFA + cohort was characterized by younger participants who showed a significantly higher percentage of *APOE*-ε4 carriers compared to the other cohorts. Participants from both ALFA + and EPAD LCS cohorts reported significantly better sleep quality compared to the FACEHBI cohort (Supplementary Table 4). However, the cohorts showed no statistically significant differences in Aβ PET values at baseline (Supplementary Table 4).

Associations between subjective sleep quality and amyloid burden.

An LME model (Model 1 in Table 2 and Supplementary Table 5) was fitted to examine the relationship between self-reported sleep quality and Aβ accumulation over time. The PSQI global score was not significantly associated with Aβ burden at baseline (β = 0.12, CI = [−0.41, 0.66], $p = 0.658$), and the interaction of PSQI global score with time was not significant (β = 0.04, CI = [−0.04, 0.11], $p = 0.352$) (Table 2).

However, when the triple interaction term time × sleep quality × baseline Aβ status was included in Model 2 (Table 2 and Supplementary Table 6), a significant interaction effect of the baseline Aβ PET category on the relationship between self-reported sleep quality and Aβ accumulation over time was found ($p = 0.001$). Among participants in the GZ group, worse self-reported sleep quality was associated with faster Aβ accumulation compared to the A- group (β = 0.22 CL/year per PSQI point, CI = [0.04, 0.41], $p = 0.017$). In contrast, for A+ participants, worse sleep quality was associated with slower Aβ accumulation relative to the A- group (β = −0.41 CL/year per PSQI point, CI = [−0.73, −0.10], $p = 0.010$) (Fig. 1).

Table 2 LME models. Main results from Model 1, testing the association between self-reported sleep quality and amyloid accumulation over time and Model 2, testing the interaction effect of the baseline amyloid category in that relationship. See supplementary information for more details on the other variables of the models

	Amyloid burden		
Predictors	**Estimates**	**CI**	***p* value**
Model 1			
PSQI	0.12	[−0.41, 0.66]	0.658
PSQI x visit years	0.04	[−0.04, 0.11]	0.352
Model 2			
PSQI x visit years x [GZ]	0.22	[0.04, 0.41]	0.017 *
PSQI x visit years x [A+]	−0.41	[−0.73, −0.10]	0.010 *

Models adjusted for age, sex, *APOE* status, cohort and presence of anxiety or depression. * $p < 0.05$

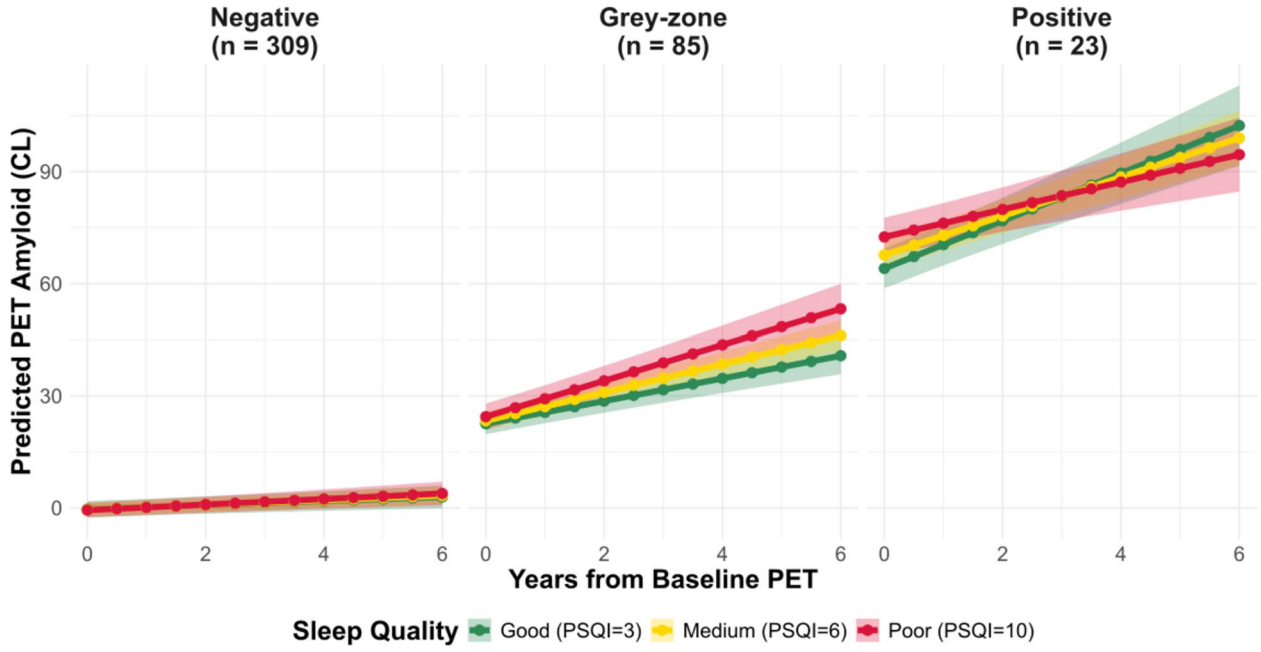

Fig. 1 Model-Predicted Amyloid Trajectories by Sleep Quality. Plot shows different predicted trajectories of amyloid accumulation depending on the baseline amyloid status and three representative levels of self-reported sleep quality, which correspond to the median of each tertile of PSQI values. Predictions from mixed-effects model with 95% confidence intervals. Color codes for three representative values of the PSQI global score tertiles

Table 3 Stratified results

	Amyloid burden		
Predictors	**Estimates**	**CI**	***p* value**
Amyloid negative (*N* = 309)			
PSQI x visit years	0.03	[−0.04, 0.09]	0.395
Grey-zone (*N* = 85)			
PSQI x visit years	0.28	[0.06, 0.50]	0.013 *
Amyloid positive (*N* = 23)			
PSQI x visit years	−0.29	[−0.77, 0.19]	0.232

Models adjusted for age, sex, *APOE* status, cohort and presence of anxiety or depression. * $p < 0.05$

Stratified analyses within each baseline Aβ category were run to further examine the association between self-reported sleep quality and the Aβ accumulation over time (Table 3). Worse sleep quality predicted faster Aβ accumulation in individuals with intermediate baseline amyloid burden categorized in the GZ group (β = 0.28, CI = [0.06, 0.50], $p = 0.013$).

Table 3 *Stratified results on the LME model* exploring the relationship between self-reported sleep quality and Aβ burden over time in each baseline amyloid PET category subsample.

Given the small number of participants in the A+ category, we ran a sensitivity analysis excluding them to rule out that the interaction with baseline amyloid category was driven by a small number of participants. As shown in the Supplementary Table 7, even without the participants of the A+ category, the interaction with the baseline Aβ category remained significant: for participants in the GZ group, worse self-reported sleep quality was associated with faster Aβ accumulation compared to the A- group (β = 0.24 CL/year per PSQI point, CI = [0.06, 0.42], $p = 0.009$).

Moreover, excluding participants with either anxiety or depression again did not alter the main findings. As shown in Supplementary Table 8, among participants without anxiety or depression, those in the GZ group at baseline showed a statistically significant positive association between worse self-reported sleep quality and a faster Aβ accumulation compared to the A- group (β = 0.22 CL/year per PSQI point, CI = [0.00, 0.43], $p = 0.045$). For the A+ group, however, only a trend remained for the association of worse self-reported sleep quality and lower Aβ accumulation compared to the A- group (β = −0.35 CL/year per PSQI point, CI = [−0.73, 0.04], $p = 0.082$).

Discussion

The aim of this study was to investigate whether self-reported poor sleep quality was associated with greater Aβ burden over time, using Aβ PET scans in a large multi-center cohort of clinically unimpaired individuals. The AMYPAD PNHS cohort offers longitudinal PET data for an unprecedented large number of cognitively healthy adults, enabling us to investigate the relationship between sleep quality and Aβ burden not only cross-sectionally but also longitudinally during the preclinical stage of AD.

Our main conclusion is that worse self-reported sleep quality at baseline is associated with an increased rate of Aβ accumulation over time only in individuals with intermediate baseline Aβ levels (i.e., those who have begun accumulating amyloid but are still in the grey zone). Paradoxically, we observed an unexpected association whereby poorer self-reported sleep quality at baseline was linked to a lower Aβ accumulation over time, only in individuals who were amyloid-positive at baseline.

Cross-sectionally, we did not observe an association between self-reported sleep quality and Aβ burden. The total PSQI score, used as a global measure of sleep quality, may not capture specific sleep features that are more closely linked to Aβ burden. This interpretation is supported by a previous study showing that longer self-reported sleep latency was associated with higher brain Aβ levels, but this relationship was not observed when using the total PSQI score [43]. This suggests that certain components of subjective sleep quality, rather than an aggregate score, might be more sensitive to detecting early Aβ changes.

Longitudinally, poor subjective sleep quality was associated with a higher Aβ accumulation over time only in individuals with intermediate Aβ deposition levels at baseline (between 12 and 50 CL), supporting the hypothesis that sleep disturbances may promote Aβ accumulation. This association remained significant after removing participants classified as Aβ positive at baseline or participants with anxiety or depression. The absence of association in the A- individuals may reflect the limited Aβ accumulation at early stages. Interestingly, the interaction analyses suggested that the relationship between self-reported sleep quality and Aβ accumulation over time is reversed in the A+ group, with those reporting better sleep quality showing the highest rates of Aβ accumulation over time. This association did not reach statistical significance in the A+ group in stratified analyses and remained only as a trend when removing participants with anxiety or depression, possibly reflecting the limited sample size within this subgroup. One possible explanation is that subjective sleep reports become less reliable due to emerging memory impairments in individuals closer to the onset of overt cognitive decline, as suggested by previous findings in individuals with mild cognitive symptoms [61]. Alternatively, the results may be influenced by a plateau effect on amyloid accumulation among participants further along the AD continuum (i.e., A+ individuals with poorer sleep quality) [62]. However, the similar magnitude of intraindividual amyloid increases observed in grey zone and A+ participants suggests that this explanation is unlikely to fully account for the present results. Another possible explanation would be a potential selection bias favoring more resilient individuals within the A+ group with poor sleep, as those with greater cognitive impairment may have not met the study inclusion criteria. Given the limited sample size in the A+ group, these findings should be interpreted with caution. Replication in independent cohorts is necessary, and the results should be considered hypothesis-generating rather than confirmatory.

The stratified analyses showed a rate of amyloid accumulation of 0.28 CL/year per PSQI point (95% CI 0.06–0.50) for the GZ group. To contextualize this magnitude, a 3-point difference in PSQI — approximately one standard deviation — would correspond to ~ 0.84 CL/year higher amyloid accumulation in the GZ group. According to previous work in the AMYPAD PNHS cohort, reliable amyloid accumulation has been estimated to occur at rates above 3.0 CL/year [54]. Against this benchmark, the effect of a one-SD difference in PSQI represents roughly 28% of that accumulation threshold, which on its own may be considered a modest contribution. However, sleep disturbance is unlikely to operate in isolation; rather, its effect may be clinically meaningful when it compounds with other modifiable risk factors — each individually modest — that together drive accumulation above the threshold for detectable progression, consistent with the multifactorial nature of preclinical AD risk.

These findings highlight poor sleep quality as a potentially modifiable risk factor for AD and suggest that clinically unimpaired individuals with intermediate Aβ levels may represent an optimal target population for preventive interventions. From a clinical trial perspective, this group could be operationalized using centiloid ranges (e.g., 12–50 CL) combined with evidence of poor sleep quality (e.g., PSQI > 5) as inclusion criteria. Interventions aimed at improving sleep in this population may help disrupt the cycle between sleep disruption and accelerated Aβ accumulation. In this context, longitudinal change in amyloid burden (e.g., reduction in CL/year slope relative to control) could serve as a primary outcome. Furthermore, objective sleep measures—particularly slow-wave sleep—may provide both mechanistic insight and utility as biomarkers of target engagement. Specifically, deficient slow-wave sleep may reflect impaired glymphatic clearance of Aβ [28, 31] and thus be associated with increased rates of amyloid accumulation over time. This hypothesis warrants testing in experimental studies in which sleep is not only assessed at baseline but actively manipulated, enabling causal inference.

While numerous studies have explored the cross-sectional relationship between subjective sleep quality and Aβ burden in healthy individuals [42, 43, 45, 63], our study advances the field by incorporating longitudinal PET data. This allowed us to track Aβ accumulation over time and examine how baseline Aβ levels modulate the link between baseline subjective sleep quality

and Aβ dynamics. Such insights are crucial for refining inclusion criteria in future clinical trials targeting sleep interventions.

The increase in Aβ burden over time during the preclinical phase of AD has already been associated with other circadian rhythms or sleep disturbances consistently with our findings: for example, excessive daytime sleepiness, as measured by the Epworth Sleepiness Scale, has been associated with increased Aβ accumulation over time, with a more pronounced effect in individuals already identified as Aβ-positive [64, 65]. Moreover, other longitudinal studies using objective sleep measures such as actigraphy or polysomnography further support this relationship, and found, for instance, that sleep fragmentation was associated with greater Aβ load over a period of 7–8 years, independent of baseline CSF Aβ levels, in cognitively normal individuals [66]. Similarly, both reductions in non-rapid eye movement slow-wave activity below 1 Hz and decreased sleep efficiency have been found to predict a steeper trajectory of Aβ deposition [67]. Finally, longitudinal associations between annual Aβ accumulation and greater day-to-day variability in sleep efficiency have been found, also reporting an impact of baseline Aβ levels on their results [68].

One of the strengths of this study lies in the use of the multi-center AMYPAD cohort, which includes participants from diverse European backgrounds. The harmonization of PET data across different scanners and tracers [49, 69] enhances the robustness and generalizability of our findings, minimizing methodological biases.

Nonetheless, our study has limitations. Sleep quality was assessed solely through self-reported measures (PSQI), which, although widely used and standardized, may be influenced by cognitive decline [61, 70]. Ideally, incorporating objective sleep measures, such as actigraphy or polysomnography, would offer a more comprehensive insight into the specific sleep disturbances contributing to Aβ pathology, while minimizing the confounding effect of early memory symptoms, and in the particular case of polysomnography, it would additionally provide information on the presence of apneas, which have been associated with cognitive decline [71] and impaired clearance [72]. Moreover, individual components from the PSQI questionnaire (especially those related to sleep duration, latency, efficiency, or sleep medication use) should be used for a more accurate interpretation of the results. PSQI measures were available only cross-sectionally; thus, the lack of longitudinal sleep data may have led to misclassification of transient sleep disturbances as stable traits, limiting the interpretation of the longitudinal associations reported herein. Information about the medication use, as well as lifestyle or vascular risk factors that could influence not only sleep quality but also Aβ accumulation was not available for this study, representing a limitation that future studies should aim to address. It is worth noting that the two main variables of interest — sleep quality and amyloid burden — were assessed using highly consistent methods across cohorts. Sleep quality was measured with the PSQI questionnaire in all participants, a standardized and widely validated instrument, while amyloid burden was estimated through PET imaging following a rigorous harmonization pipeline. This methodological consistency ensures that the key variables are highly comparable across cohorts, minimizing the risk that cohort differences drive the observed associations. That said, cohorts differed in other relevant characteristics, and including cohort as a fixed effect in our models may attenuate but not fully eliminate the potential confounding effects of pooling data from different sources. Further studies should aim to integrate both subjective and objective sleep assessments to disentangle the precise sleep characteristics associated with Aβ accumulation. This dual approach will be essential for developing targeted sleep interventions aimed at slowing Aβ progression and ultimately, delaying cognitive decline associated with AD.

Conclusions

This study found that poor subjective sleep quality is associated with an increased amyloid burden over time only when individuals show intermediate Aβ deposition levels at baseline (between 12 and 50 CL). These findings identify a critical therapeutic window that could optimize patient selection and enhance the efficacy of sleep-targeted interventions in future clinical trials.

Abbreviations

A-	Amyloid negative
A+	Amyloid positive
AD	Alzheimer's Disease
ALFA	ALzheimer and FAmilies
AMYPAD PNHS	Amyloid Imaging to Prevent Alzheimer's Disease – Prognostic and Natural History Study
ANOVA	Analysis of Variance
APOE	Apolipoprotein E
Aβ	Amyloid-β
BMI	Body Mass Index
CDR	Clinical Dementia Rating
CI	Confidence Interval
CL	Centiloid
CSF	Cerebrospinal Fluid
CU	Clinically Unimpaired
EPAD LCS	European Prevention of Alzheimer's Dementia Longitudinal Cohort Study
FACEHBI	Fundació ACE Healthy Brain Initiative
GDS	Geriatric Depression Scale
GZ	Grey-Zone
HADS	Hospital Anxiety and Depression Scales
HSD	Tukey's Honestly Significant Difference
LME	Linear Mixed-Effects
PET	Positron Emission Tomography
PSQI	Pittsburgh Sleep Quality Index
SEM	Standard Error of the Mean
STAI	State-Trait Anxiety Inventory

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-026-02049-w.

Supplementary Material 1.

Acknowledgements

The authors would like to express their thanks to the AMYPAD PNHS participants, without whom this research would not have been possible, to Wiesje Van Der Flier for her valuable contributions to the project, and to Helena Palma-Gudiel, for guidance during the manuscript submission process. * Data used in the preparation of this article was obtained from the Prognostic and Natural History Study (PNHS), provided by the Amyloid Imaging to Prevent Alzheimer's Disease Consortium (AMYPAD). As such, investigators within the AMYPAD PNHS and AMYPAD Consortium contributed to the design and implementation of AMYPAD and/or provided data but did not participate in the analysis or writing of this report. A complete list of AMYPAD investigators can be found at https://doi.org/https://doi.org/10.5281/zenodo.7962737

Author's contributions

OGR and NTC designed the study. NTC wrote the first draft of the manuscript, analyzed, and interpreted data. OGR, NSD and DVG contributed to data interpretation. OGR, GSB and AFA contributed to manuscript writing. All authors critically revised the manuscript and approved its content before submission.

Funding

OG-R received support from the grant IJC2020-043417-I, funded by MCIN/AEI/https://doi.org/10.13039/501100011033 and the European Union NextGenerationEU/PRTR; this study has been funded by Instituto de Salud Carlos III (ISCIII) through the projects "PI19/00117" and "PI24/00116", co-funded by the European Union/FEDER, and through the project "CB16/10/00417" (OG-R).

GS-B receives support from the grant CP23/00039 (Miguel Servet), funded by the Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union/FSE+, and receives funding from the MCIN/AEI/https://doi.org/10.13039/501100011033 through the project PID2020-119556RA-I00 and through the project PID2024-163071OB-I00, funded by MICIU/AEI/https://doi.org/10.13039/501100011033 and by the European Union FEDER.

This work used data from AMYPAD PNHS that has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115952. This Joint Undertaking received support from the European Union's Horizon 2020 research and innovation program and EFPIA. This communication reflects the views of the authors and neither IMI nor the European Union and EFPIA are liable for any use that may be made of the information contained herein.

The FACEHBI study was supported with funds from Ace Alzheimer Center Barcelona, Life Molecular Imaging, Grifols, Araclon Biotech, Alkahest, Laboratorio de análisis Echevarne, and IrsiCaixa. The FACEHBI study was part of the AMYPAD-PNHS project, which received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115952. MB received funding support from CIBERNED (Instituto de Salud Carlos III (ISCIII); EU/EFPIA Innovative Medicines Initiative Joint Undertaking, ADAPTED Grant No. 115975; EXIT project, EU Euronanomed3 Program JCT2017 Grant No. AC17/00100; MOPEAD, Innovative Medicine Initiative, Grant. Nº. 115,985; PreDADQoL, ERA-NET (call 2015). Grant nº AC15/00082; TARTAGLIA (Red federada para acelerar la aplicación de la inteligencia artificial en el sistema sanitario español); PREADAPT project, Joint Program for Neurodegenerative Diseases (JPND) Grant No. AC19/00097; GECONEU Grant No. 2023–1-ELO1-KAZZ0-HED-000032173 co –founded by the European Union; Grants PI13/02434, PI16/01861, BA19/00020, and PI19/01301 from the Acción Estratégica en Salud, integrated in the Spanish National RCDCI Plan and financed by Instituto de Salud Carlos III (ISCIII)- Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER – "Una manera de Hacer Europa"); Fundació "La Caixa" and Grifols (GR@ACE project); and Proyectos de Investigación de Medicina Personalizada (ISCIII), PMP-DEGESCO, Grant Nº PMP22/00022. MM has received funding support from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement no. 796706, and the Instituto de Salud Carlos III (ISCIII) Acción Estratégica en Salud, integrated in the Spanish National RCDCI Plan and financed by ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER—Una manera de hacer Europa) grant PI19/00335.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The AMYPAD project was reviewed and approved by Medical Ethical Committee of the University Medical Center Amsterdam, location VUmc and all local sites. The AMYPAD PNHS is registered on the EU Clinical Trials Register with the EudraCT Number: 2018–002277-22. The study was conducted following the Protocol and the Declaration of Helsinki and Good Clinical Practice. All patients/participants provided written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

OGR receives research funding from F. Hoffmann-La Roche Ltd and has given lectures in symposia sponsored by Roche Diagnostics and Idorsia Pharmaceuticals Ltd., S.L.U. GS-B worked as a consultant for Roche Farma, S.A. JDG has received research support from GE HealthCare, Roche Diagnostics, and Hoffmann – La Roche; has received speaker/consulting fees from Roche Diagnostics, Philips Netherlands, Esteve, Biogen, and Life Molecular Imaging; served in the Molecular Neuroimaging Advisory Board of Prothena Biosciences; and is founder and co-owner of BetaScreen SL. He is currently a full-time employee of AstraZeneca. MB has consulted for Grifols, Araclon Biotech, Roche, Biogen, Lilly, Merck, Novo-Nordisk; has served in the Advisory Boards from Grifols, Roche, Lilly, Araclon Biotech, Merck, Biogen, Novo-Nordisk, Bioiberica, Eisai, Servier, Schwabe Pharma; received fees from lectures from Roche, Biogen, Grifols, Nutricia, Araclon Biotech, Novo-Nordisk, Eisai, Terumo, Schwabe Pharma; and reports research funding from Life Molecular Imaging, Bioiberica, Grifols, Araclon Biotech, Lilly, Roche, Janssen, Alzehon, Cortyzime, Novo Nordisk, Schwabe Pharma. MM has consulted for F. Hoffmann-La Roche Ltd. and has served in the Spanish Scientific Advisory Board for biomarkers of Araclon Biotech. The remaining authors declare that they have no competing interests.

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Received: 5 February 2026 / Accepted: 3 April 2026
Published online: 17 April 2026

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