

BRIEF COMMUNICATION

Subjective sleep parameters in prodromal Alzheimer's disease: a case-control study

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Objective: People with Alzheimer's disease (AD) dementia have impaired sleep. However, the characteristics of sleep in the early stages of AD are not well known, and studies with the aid of biomarkers are lacking. We assessed the subjective sleep characteristics of non-demented older adults and compared their amyloid profiles.

Methods: We enrolled 30 participants aged ≥ 60 years, with no dementia or major clinical and psychiatric diseases. They underwent [¹¹C]PIB-PET-CT, neuropsychological evaluations, and completed two standardized sleep assessments (Pittsburgh Sleep Quality Inventory and Epworth Sleep Scale).

Results: Comparative analysis of subjective sleep parameters across the two groups showed longer times in bed ($p = 0.024$) and reduced sleep efficiency ($p = 0.05$) in individuals with positive amyloid. No differences in other subjective sleep parameters were observed. We also found that people with multiple-domain mild cognitive impairment (MCI) had shorter self-reported total sleep times ($p = 0.034$) and worse overall sleep quality ($p = 0.027$) compared to those with single-domain MCI.

Conclusions: Older adults testing positive for amyloid had a longer time in bed and lower sleep efficiency, regardless of cognitive status. In parallel, individuals with multiple-domain MCI reported shorter sleep duration and lower overall sleep quality.

Keywords: Sleep; mild cognitive impairment; pre-clinical Alzheimer's disease; positron emission tomography

Introduction

Recently, researchers have shifted their attention to preclinical phases of Alzheimer's disease (AD). Studies addressing interactions between sleep and AD have brought evidence on the specific sleep characteristics of people with mild cognitive impairment (MCI)¹⁻⁴ and subjective cognitive decline (SCD).^{5,6} However, the diagnosis of AD guided by clinical criteria alone has low agreement with pathologic diagnosis, especially in people with milder cognitive disturbances. The use of biomarkers improves diagnostic accuracy for AD dementia, and enables a better diagnosis of prodromal and preclinical AD.

Although some studies have explored the sleep characteristics of people with MCI and SCD using subjective and objective methods, few of them have assessed such characteristics after ascertaining the AD biomarker profiles of the subjects.⁷⁻⁹ This study aims to investigate the association between subjective sleep characteristics and amyloid profile in people with MCI and SCD as opposed to cognitively unimpaired older adults.

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Methods

Setting and participants

This is a cross-sectional study, part of a Brazilian community-based cohort.

We included 30 participants aged ≥ 60 years. Exclusion criteria were: functional impairment, history of major psychiatric disorders, major neurologic diseases, decompensated clinical diseases, use of sleep inducers or antipsychotic drugs, and brain magnetic resonance imaging showing vascular lesions or a score > 2 on the Fazekas scale.¹⁰

Study design

All participants underwent a throughout clinical evaluation for assessment of demographics, previous medical history, cognitive complaints, and socioeconomic classification. In the first interview, they underwent cognitive screening and completed the Hospital Anxiety and Depression Scale (HAD)¹¹ and Functional Activities

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Questionnaire.¹² Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI),¹³ and excessive daytime sleepiness by the Epworth Sleepiness Scale (ESS).¹⁴

Neuropsychological assessment

After this first interview, the participants underwent a comprehensive neuropsychological assessment. The cognitive domains evaluated were executive functions, attention, verbal and nonverbal memory, language, and visuospatial function.

Group allocation

Group allocation was based on the clinical evaluation and the neuropsychological assessment. The individuals were classified as MCI if they remained functionally independent and had a performance worse than one standard deviation (SD) below the mean¹⁵ in two tests of the same cognitive domain. They were subclassified as MCI-single domain (MCI-SD) if only one domain was affected and as MCI-multiple domain (MCI-MD) if two or more domains were affected. Participants were classified as SCD if they had cognitive complaints but a normal neuropsychological evaluation, and as cognitively unimpaired (CUn) if they had a normal neuropsychological evaluation without cognitive complaints.

[¹¹C]PiB-PET categories

All subjects had undergone a positron emission tomography with Pittsburgh compound ([¹¹C]PiB-PET-CT) no more than 1 year before the study. Production of the [¹¹C]PiB-PET radiochemical has been described in detail elsewhere.¹⁶

Two certified nuclear medicine physicians with more than 5 years of experience evaluated the [¹¹C]PiB-PET images, blinded to clinical diagnosis and to the other's interpretation. They independently rated the individual images as "positive" (A+) and "negative" (A-). At a second time point, each physician performed a semi-quantitative analysis with the aid of the 3D-SSP method to confirm the qualitative analysis. Our group has described this procedure in further detail elsewhere.¹⁷

Subjective Sleep Questionnaires

During sleep evaluations, participants were assessed with the PSQI.¹³ As measures of sleep quality, we extracted

data from the PSQI's sub-items: sleep onset latency (SOL), subjective report of total sleep time (sr-TST), time in bed (TIB), and sleep efficiency (SE), besides the PSQI total score (PSQI). The ESS – a questionnaire that classifies subjective daytime sleepiness – was used as a measure of daytime sleepiness.¹⁸

Statistical analysis

We described the characteristics of participants using means/standard deviations, medians/interquartile ranges, or counts and percentages, as appropriate. We used the Mann-Whitney test to compare sleep variables across the amyloid A+ and A- groups and the Kruskal-Wallis test, followed by Bonferroni's test, to compare the sleep variables across the four clinically classified groups. Differences were considered as statistically significant if a two-tailed $p \leq 0.05$.

Ethics statement

The local ethics committee approved this study, and all participants provided written informed consent.

Results

Thirty subjects were evaluated, of whom 21 (67.7%) were female. The mean age was 73 years (SD = 5.92), and the mean educational level was 13 years (SD = 4.93).

Nine individuals (31%) were amyloid-positive on PiB-PET. They had fewer years of schooling and more depressive symptoms (HAD-D) than their amyloid-negative peers. The groups did not differ in age, sex, BMI, vascular risk factors, hypothyroidism, anxiety scores (HAD-A), or socioeconomic status.

Comparative analysis of subjective sleep parameters between the A+ and A- groups revealed longer TIB ($p = 0.024$) and lower SE ($p = 0.05$) in A+ individuals, and no differences in SOL, sr-TST, PSQI, or ESS (Table 1).

Comparison of subjective sleep parameters across the clinical categories (CUn, SCD, MCI-SD and, MCI-MD) revealed between-group differences in sr-TST and PSQI-s, but not in the other sleep variables. Post-hoc analysis showed lower sr-TST and higher PSQI in MCI-MD compared to MCI-UD (Table 2).

Table 1 Comparison of sleep parameters between the amyloid-positive (A+) and amyloid-negative (A-) groups

	A+ (n=9)	A- (n=20)	p-value
SOL	23.3 (18.5)	11.9 (13.3)	0.74
Sr-TST	6.1 (1.3)	6.4 (1.1)	0.57
TIB	8.2 (1.0)	7.2 (1.1)	0.024*
SE	75.7 (14.9)	90.9 (16.5)	0.05*
PSQI	5.8 (3.0)	4 (2.2)	0.11
ESS	5.9 (2.6)	4.8 (4.2)	0.25

* Significant two-tailed $p \leq 0.05$.

ESS = Epworth Sleep Scale (total score); PSQI = Pittsburgh Sleep Quality Index (total score); SE = sleep efficiency; SOL = sleep onset latency; sr-TST = self-reported total sleep time; TIB = time in bed.

Table 2 Comparison of subjective sleep parameters among the groups CUn, SCD, MCI-SD, and MCI-MD

	CUn (n=7)	SCD (n=8)	MCI-SD (n=8)	MCI-MD (n=7)	p-value
SOL	16.0 (19.8)	7.5 (6.3)	15.0 (10.0)	24.6 (20.3)	0.16
sr-TST	6.4 (0.9)	6.6 (0.9)	7.2 (0.9)*	5.3 (1.2)*	0.03 [‡]
TIB	7.3 (1.1)	7.4 (1.2)	7.9 (1.2)	7.6 (1.5)	0.81
SE	87.6 (9.1)	89.5 (9.7)	93.0 (18.0)	73.5 (23.7)	0.06
PSQI	3.9 (1.1)	3.6 (2.3)	3.4 (1.8) [†]	7.4 (2.7) [†]	0.03 [‡]
ESS	5.5 (4.5)	5.6 (4.8)	3.1 (2.6)	6.7 (2.0)	0.21

CUn = cognitively unimpaired; ESS = Epworth Sleep Scale (total score); MCI-MD = mild cognitive impairment- multiple domain; MCI-SD = mild cognitive impairment-single domain; PSQI = Pittsburgh Sleep Quality Index (total score); SCD = subjective cognitive decline; SE = sleep efficiency; SOL = sleep onset latency; sr-TST = self-reported total sleep time; TIB = time in bed.

Analysis showed:

* A difference in sr-TST between the MCI-UD and MCI-MD groups (adjusted two-tailed $p = 0.021$)

[†] A difference in PSQI between the MCI-MD and MCI-SD groups (adjusted two-tailed $p = 0.038$).

[‡] Significant two-tailed $p \leq 0.05$.

Discussion

To our knowledge, this is the first study to assess subjective sleep parameters in individuals with MCI, according to amyloid status and single- or multiple-domain cognitive impairment. In this sample, A+ subjects showed longer TIB and lower SE.

Few similar studies do exist. One study with [¹¹C]PiB-PET found higher amyloid loads in several brain areas of old adults with shorter self-reported sleep duration and impaired sleep quality.⁷

Another study found that middle-aged and older adults with reduced amyloid levels in the cerebrospinal fluid had low SE and a trend toward increased TIB on actigraphy,⁸ corroborating our data. According to this hypothesis, increased amyloid loads would disrupt normal sleep physiology, leading to more fragmented sleep, demanding longer times in bed as compensation for decreased sleep quality.

Amyloid positivity was not associated with increased ESS scores in our sample, which would be more likely. Two recent studies have shown similar results in this test, but more somnolence in A+ individuals in another test.^{9,19} One possible explanation is that ESS asks about the propensity of the subject falling asleep during the day, which is less sensitive than questionnaires that ask specifically about daytime sleepiness.

According to our review of the literature, this is the second study to highlight sleep differences between individuals with multiple-domain versus single-domain MCI. Most of the studies that included MCI subgroups divided them into amnesic and non-amnesic, and did not take into account whether there was a multidomain disorder.⁴

Studies have diverged concerning the total sleep time of individuals with MCI. Differently from our results, some of them have associated longer sleep times with reduced cognitive performance.^{3,20}

The use of a subjective sleep assessment could explain the lower sleep duration shown by our MCI-MD participants. One study found that people with MCI reported shorter sleep times and worse sleep quality when compared with data obtained by objective methods.²¹

The sleep quality reduction in people with MCI-MD shown by our study, as measured by the PSQI score, corroborates the current literature.^{2,4,22}

In our study, individuals with an SCD diagnosis did not differ from CUn in the subjective sleep measures; this diverges from recent studies that found worse sleep quality in people with subjective cognitive complaints.^{5,6}

We did not find reduced educational attainment in individuals with MCI, which disagrees with previous studies showing an association of worse overall sleep quality with lower educational levels.² However, we found that A+ subjects had lower educational levels than their A- peers. We intend to address this matter in future research.

In this study, A+ participants had significantly higher HAD-D scores in comparison to A- subjects, despite not crossing the thresholds of normality. One possible explanation is that people in the earlier stages of AD exhibit depressive symptoms more frequently.^{23,24} Also, some studies have associated early-life depressive symptoms with an increased risk of cognitive impairment and AD later in life.²⁵

This study's strengths are the determination of amyloid profiles with PiB-PET to classify groups, the use of widely disseminated, standardized sleep scales to assess sleep, and the classification of MCI by the number of domains instead of into amnesic/non-amnesic.

Some limitations must also be discussed. We evaluated a small number of subjects, which prevented the subdivision of clinical categories according to the amyloid profile. The characteristics of the sample diverge from the overall population of the city where it was conducted, which can limit the validity of the study to one specific population segment. Finally, the cross-sectional design prevents the establishment of causal relationships.

In conclusion, older adults with positivity for amyloid had a longer time in bed and lower sleep efficiency, regardless of cognitive status. Likewise, individuals with MCI-MD subjectively reported shorter sleep duration and lower overall sleep quality. More extensive, prospective studies using objective sleep measurements to accurately characterize the sleep of individuals in the preclinical stages of AD – defined by biomarkers, clinical indicators, or both – are welcome. The identification of more severe MCI phenotypes may involve detection of poor sleep.

Disclosure

The authors report no conflicts of interest.

References

- 1 Hita-Yanez E, Aienza M, Gil-Neciga E, Cantero J. Disturbed sleep patterns in elders with mild cognitive impairment: the role of memory decline and Apoe E ε4 genotype. *Curr Alzheimer Res.* 2012;9:290-7.
- 2 Seidel S, Dal-Bianco P, Pablik E, Müller N, Schadenhofer C, Lamm C, et al. Depressive symptoms are the main predictor for subjective sleep quality in patients with mild cognitive impairment – a controlled study. *PLoS One.* 2015;10:e0128139.
- 3 Spira AP, Stone KL, Redline S, Ensrud KE, Ancoli-Israel S, Cauley JA, et al. Actigraphic sleep duration and fragmentation in older women: associations with performance across cognitive domains. *Sleep.* 2017;40:zsx073.
- 4 Hayes TL, Riley T, Mattek N, Pavel M, Kaye JA. Sleep habits in mild cognitive impairment. *Alzheimer Dis Assoc Disord.* 2014;28:145-50.
- 5 Lee JE, Ju YJ, Park EC, Lee SY. Effect of poor sleep quality on subjective cognitive decline (SCD) or SCD-related functional difficulties: results from 220,000 nationwide general populations without dementia. *J Affect Disord.* 2020;260:32-7.
- 6 Tsapanou A, Vlachos GS, Cosentino S, Gu Y, Manly JJ, Brickman AM, et al. Sleep and subjective cognitive decline in cognitively healthy elderly: results from two cohorts. *J Sleep Res.* 2019;28:e12759.
- 7 Spira AP, Gamaldo AA, An Y, Wu MN, Simonsick EM, Bilgel M, et al. Self-reported sleep and β-amyloid deposition in community-dwelling older adults. *JAMA Neurol.* 2013;70:1537-43.
- 8 Ju YE, McLeland JS, Toedebusch CD, Xiong C, Fagan AM, Duntley SP, et al. Sleep quality and preclinical Alzheimer disease. *JAMA Neurol.* 2013;70:587-93.
- 9 Sprecher KE, Kosciak RL, Carlsson CM, Zetterberg H, Blennow K, Okonkwo OC, et al. Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults. *Neurology.* 2017;89:445-53.
- 10 Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Neuroradiol.* 1987;8:421-6.
- 11 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* 1983;67:361-70.
- 12 Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol.* 1982;37:323-9.
- 13 Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28:193-213.
- 14 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14:540-5.
- 15 Jak AJ, Bondi MW, Delano-Wood L, Wierenga C, Corey-Bloom J, Salmon DP, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. *Am J Geriatr Psychiatry.* 2009;17:368-75.
- 16 Faria DP, Duran FL, Squarzone P, Coutinho AM, Garcez AT, Santos PP, et al. Topography of 11c-pittsburgh compound b uptake in Alzheimer's disease: a voxel-based investigation of cortical and white matter regions. *Braz J Psychiatry.* 2019;41:101-11.
- 17 Coutinho AM, Busatto GF, Porto FH, Faria DP, Ono CR, Garcez AT, et al. Brain PET amyloid and neurodegeneration biomarkers in the context of the 2018 NIA-AA research framework: an individual approach exploring clinical-biomarker mismatches and socio-demographic parameters. *Eur J Nucl Med Mol Imaging.* 2020;47:2666-80.
- 18 Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep.* 1992;15:376-81.
- 19 Sprecher KE, Bendlin BB, Racine AM, Okonkwo OC, Christian BT, Kosciak RL, et al. Amyloid burden is associated with self-reported sleep in nondemented late middle-aged adults. *Neurobiol Aging.* 2015;36:2568-76.
- 20 Basta M, Simos P, Vgontzas A, Koutentaki E, Tziraki S, Zaganas I, et al. Associations between sleep duration and cognitive impairment in mild cognitive impairment. *J Sleep Res.* 2019;28:e12864.
- 21 Hita-Yañez E, Aienza M, Cantero JL. Polysomnographic and subjective sleep markers of mild cognitive impairment. *Sleep.* 2013;36:1327-34.
- 22 Westerberg CE, Mander BA, Florczak SM, Weintraub S, Mesulam MM, Zee PC, et al. Concurrent impairments in sleep and memory in amnesic mild cognitive impairment. *J Int Neuropsychol Soc.* 2012;18:490-500.
- 23 Tan EY, Köhler S, Hamel RE, Muñoz-Sánchez JL, Verhey FR, Ramakers IH. Depressive symptoms in mild cognitive impairment and the risk of dementia: a systematic review and comparative meta-analysis of clinical and community-based studies. *J Alzheimer's Dis.* 2019;67:1319-29.
- 24 Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? *Maturitas.* 2014;79:184-90.
- 25 Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry.* 2006;63:530-8.