

Original Article



# Relationship Between Amyloid Positivity and Sleep Characteristics in the Elderly With Subjective Cognitive Decline

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## ABSTRACT


**Background and Purpose:** Alzheimer's disease (AD) is a neurodegenerative disease characterized by a progressive decline in cognition and performance of daily activities. Recent studies have attempted to establish the relationship between AD and sleep. It is believed that patients with AD pathology show altered sleep characteristics years before clinical symptoms appear. This study evaluated the differences in sleep characteristics between cognitively asymptomatic patients with and without some amyloid burden.

**Methods:** Sleep characteristics of 76 subjects aged 60 years or older who were diagnosed with subjective cognitive decline (SCD) but not mild cognitive impairment (MCI) or AD were measured using Fitbit® Alta HR, a wristwatch-shaped wearable device. Amyloid deposition was evaluated using brain amyloid plaque load (BAPL) and global standardized uptake value ratio (SUVR) from fluorine-18 florbetaben positron emission tomography. Each component of measured sleep characteristics was analyzed for statistically significant differences between the amyloid-positive group and the amyloid-negative group.

**Results:** Of the 76 subjects included in this study, 49 (64.5%) were female. The average age of the subjects was 70.72±6.09 years when the study started. 15 subjects were classified as amyloid-positive based on BAPL. The average global SUVR was 1.598±0.263 in the amyloid-positive group and 1.187±0.100 in the amyloid-negative group. Time spent in slow-wave sleep (SWS) was significantly lower in the amyloid-positive group (39.4±13.1 minutes) than in the amyloid-negative group (49.5±13.1 minutes) (p=0.009).

**Conclusions:** This study showed that SWS is different between the elderly SCD population with and without amyloid positivity. How SWS affects AD pathology requires further research.

**Keywords:** Alzheimer Disease; Cognitive Decline; Sleep, Slow-Wave

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**Conflict of Interest**

The authors have no financial conflicts of interest.

**Author Contributions**

Conceptualization: Jo KJ, Yang DW, Park KH; Data curation: Yang DW, Park KH; Formal analysis: Jo KJ, Yang DW, Park KH; Funding acquisition: Yang DW; Investigation: Yang DW, Park KH; Methodology: Yang DW, Park KH; Project administration: Yang DW, Park KH; Software: Yang DW; Supervision: Yang DW, Park KH; Validation: Yang DW, Park KH; Visualization: Yang DW, Park KH; Writing - original draft: Jo KJ, Park KH; Writing - review & editing: Ho S, Hong YJ, Jeong JH, Kim S, Wang MJ, Choi SH, Han S, Yang DW, Park KH.

**INTRODUCTION**

According to the currently accepted amyloid cascade hypothesis, the accumulation of protein aggregates such as amyloid-beta ( $A\beta$ ) and neurofibrillary tangles is a critical step in Alzheimer's disease (AD).<sup>1</sup>  $A\beta$  is a product of normal brain metabolism produced by neurons and excreted into the interstitial fluid (ISF); however, its exact function is still unclear.<sup>2</sup> AD pathogenesis begins when  $A\beta$  proteins, which are naturally soluble, aggregate and form insoluble plaques.<sup>2</sup> The brain utilizes various methods to discard such metabolites. The currently identified mechanisms include degradation via enzymatic breakdown, blood-brain barrier clearance via specialized transporters in the brain endothelium, and ISF bulk flow into the cerebrospinal fluid (CSF) sink and subsequently into the circulatory or lymphatic systems.<sup>1</sup> An imbalance between the production and removal of  $A\beta$  results in its deposition within the brain, which, according to the amyloid cascade hypothesis, manifests as cognitive decline and functional impairment over time.

Sleep is "a recurring, reversible, neuro-behavioral state of relative perceptual disengagement from and unresponsiveness to the environment."<sup>3</sup> Although the understanding of sleep is far from complete, it is presumed that sleep plays a significant role in the clearance of waste products such as  $A\beta$  from the brain.<sup>4</sup> The anatomical and neurochemical viewpoints suggest a close link between sleep and AD pathogenesis, which is corroborated by clinical observations of patients in various stages of AD. Changes in sleep are detectable long before the onset of observable AD pathology and worsen in severity as the disease progresses.<sup>5</sup> Recent research has focused on examining whether sleep, or lack thereof, has an effect on AD.

Subjective cognitive decline (SCD) is another observable entity that precedes cognitive and behavioral changes in AD. By definition, the only difference between individuals with SCD and cognitively normal individuals without SCD is whether they report feelings of cognitive impairment.<sup>6</sup> SCD is nevertheless considered a preclinical stage and a risk factor for AD.<sup>7</sup> The probability of SCD progressing to mild cognitive impairment (MCI) and AD within 5 years are 34.2% and 10.7%, respectively.<sup>8</sup> The SCD population is a heterogeneous group with various etiologies of cognitive impairment;  $A\beta$  is detected in only 12%–43% of patients with SCD.<sup>9</sup> Identifying factors that contribute to increased  $A\beta$  deposition in patients with SCD may help neurologists better understand AD pathogenesis.

Sleep disturbance in individuals with SCD may be a good starting point for investigation, as the relationship between the two harbingers of AD may offer new insights into the neurodegenerative disease at hand. Therefore, this study investigated whether the accumulation of  $A\beta$  is related to certain characteristics of sleep in the elderly with SCD. Quantifiable measurements to represent sleep were obtained via Fitbit® Alta HR, a wearable device provided by Google. SCD was evaluated using various neuropsychological tests, biochemical measurements, and amyloid image studies.

**METHODS****Patient population**

This study is a subgroup analysis of CoSCo, a multicenter prospective observational study of 120 subjects aged 60 years or older in the Republic of Korea. CoSCo was designed to establish

a cohort of elderly patients with SCD and identify risk factors that can predict progression to MCI or dementia.<sup>10</sup>

A cross-sectional study involving 76 subjects from 7 clinical institutions was conducted from October 2018 to December 2020. Subjects complained of persistent cognitive decline but did not meet the diagnostic criteria for MCI and dementia, as defined by Petersen and the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> edition (DSM-V) respectively.<sup>11</sup> Diagnostic criteria identical to that used in CoSCo were used for defining SCD,<sup>6,10</sup> which were as follows: Patients satisfying aforementioned conditions with scores greater than  $-1.5$  standard deviations from the normative mean (henceforth SD) or any neuropsychological test within a specific cognitive domain, were classified as SCD.<sup>6</sup> Patients scoring between  $-1.5$  and  $0$  SD in the memory domain and greater than  $-1.5$  SD in any cognitive domain were deemed at high risk for progressing to MCI or dementia.

Subjects aged 60 years or older with cognitive performance consistent with aforementioned definition of SCD, minimum educational attainment of elementary school graduation, and normal activities of daily living were included in the study. Among them, only those who seemed to rapidly develop into MCI or dementia, with Seoul verbal learning test (SVLT) delayed recall score between  $-1.5$  and  $0$  SD, based on the previous study results in our study team, were included in this study.<sup>12</sup> Subjects with any of the following were excluded from the study: vitamin B9 or B12 deficiency, syphilis, thyroid function abnormality, anxiety disorder, somatic symptom disorder, uncontrolled depression, schizophrenia, alcohol and substance dependence, and other identifiable, non-AD causes of cognitive impairment.

To evaluate cognitive performance, all subjects underwent assessment using the Korean version of Mini-Mental State Exam (MMSE) and Seoul Neuropsychological Screening Battery II (SNSB-II). The SNSB-II consists of the following tests: Digit Span Test (DST; forward, verbal), the Korean version of Boston naming test (K-BNT), Rey-Osterrieth complex figure test (RCFT), SVLT, digit-symbol coding (DSC), Controlled Oral Word Associated Test (COWAT), the Korean version of Trail Making Test for the Elderly, type B (K-TMT-E:B), and the Korean version of color word stroop test (K-CWST). SNSB-II scores were standardized with respect to the patient's age and educational attainment so as to compare with SNSB-II scores obtained from a nationwide Korean sample population ( $n=1,100$ ).

### Determining amyloid positivity

Immediately after enrollment, all the subjects underwent a fluorine-18 florbetaben positron emission tomography (<sup>18</sup>F-FBB PET), from which brain amyloid plaque load (BAPL) and standardized uptake value ratio (SUVR) were calculated by a trained nuclear medicine specialist in one of the participating hospital. Subjects were classified as either amyloid-positive or amyloid-negative using a dichotomized approach suggested by Barthel et al.,<sup>13</sup> where BAPL 1 was interpreted as amyloid-negative and BAPL 2 and BAPL 3 as amyloid-positive. SUVR was acquired in the same manner as in our previous study, as listed below: MATLAB version 2013a and SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>) were used to obtain the quantitative regional amyloid burden. A volume-based template with 90 regions of interest was aligned to the individual brain MRI. SUVR was obtained using whole voxels of <sup>18</sup>F-FBB PET images based on uptake in the cerebellar gray matter, which was set as a reference region.<sup>14</sup> Global SUVR was calculated as the average of 90 regional uptake values.<sup>10</sup>

### Sleep characteristics

Sleep characteristics were determined using Fitbit® Alta HR, a wearable device based on cardiorespiratory sleep staging.<sup>15</sup> Parameters that were used to quantify sleep characteristics in this study included: Total sleep time; total time spent in bed; time spent awake in bed; number of times awakened during sleep; total rapid eye movement (REM) sleep time; total time in light sleep (stages 1 and 2 of non-rapid eye movement sleep (NREM), thus NREM 1 and NREM 2); and total time in slow-wave sleep (SWS) (stage 3 of NREM, thus NREM 3). Pittsburgh Sleep Quality Index (PSQI) score was also obtained for device-independent measurement of sleep disturbance.

### Statistical analysis

Data are expressed in terms of frequency (%) or a combination of mean and standard deviation. Pearson's  $\chi^2$  test was used to analyze categorical variables. Independent samples *t*-test was used to analyze continuous variables. Age, sex, MMSE score, PSQI score, ApoE4 genotype, and previously listed parameters of sleep characteristics were compared between the amyloid-positive group and the amyloid-negative group. The correlation between global SUVR and the above variables (except age, which was used as a control variable) was also analyzed. A *p*-value of less than 0.05 was used to determine statistical significance. All statistical analysis was done using SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA).

### Ethics statement

Ethical approval for this study was obtained from the Institutional Review Board of Gachon University Gil Medical Center (Approval number GAIRB2021-097).

## RESULTS

Of the 76 subjects enrolled in this study, 49 (64.5%) were female. The average age of the subjects was 70.72±6.09 years at the beginning of the study. The number of subjects diagnosed with hypertension, diabetes, and hyperlipidemia were 32 (42.1%), 21 (27.6%), and 31 (40.8%), respectively. A total of 2 (2.6%) had a previous history of ischemic stroke, whereas none had a previous history of hemorrhagic stroke. None of the 76 subjects smoked. 15 patients (19.7%) were included in the amyloid-positive group based on BAPL. The average global SUVR was 1.27±0.22.

### Comparison between the amyloid-positive group and the amyloid-negative group

As shown in **Table 1**, time spent in SWS was significantly lower in the amyloid-positive group than in the amyloid-negative group. No other sleep parameter variables showed a statistically significant difference between the two groups.

### Age-adjusted correlation between global SUVR and dichotomous variables

As shown in **Table 2**, global SUVR was significantly higher in the ApoE4 genotype carrier group than in the non-carrier group when adjusted for age. Meanwhile, there was no statistically significant difference in global SUVR between sexes when adjusted for age.

### Age-adjusted correlation between global SUVR and continuous variables

As shown in **Table 3**, there was no statistically significant correlation between global SUVR and variables evaluated in this study when adjusted for age.

**Table 1.** Demographics and sleep parameters in relationship to amyloid positivity

Variables	Amyloid-negative (n=61)	Amyloid-positive (n=15)	p-value
Age (yr)	70.10±6.06	73.00±5.86	0.106
Sex			0.108
Male (n=27)	19 (31.1)	8 (53.3)	
Female (n=49)	42 (68.9)	7 (46.7)	
ApoE4 genotype			0.096
Carrier (n=14)	9 (14.8)	5 (33.3)	
Non-carrier (n=62)	52 (85.2)	10 (66.7)	
Hypertension	30 (49.2)	2 (13.3)	0.012
Diabetes	18 (29.5)	3 (20.0)	0.461
Hyperlipidemia	28 (45.9)	3 (20.0)	0.067
Global SUVR	1.187±0.100	1.598±0.263	<0.001
MMSE	27.20±1.97	26.90±1.92	0.600
PSQI	6.10±3.74	6.33±3.52	0.826
Sleep parameters			
Total sleep time (min)	404.0±74.8	375.0±71.0	0.172
Total time spent in bed (min)	467.0±86.6	432.0±80.3	0.156
Time spent awake in bed (min)	63.5±14.9	56.9±17.3	0.146
Number of times awakened during sleep	21.20±7.16	18.00±7.54	0.131
Total REM sleep time (min)	65.7±23.4	54.4±16.6	0.085
Total time in light sleep (min)	240.0±49.1	236.0±58.7	0.778
Total time in slow-wave sleep (min)	49.5±13.1	39.4±13.1	0.009

Values are presented as number (%) or mean ± standard deviation.

ApoE4: apolipoprotein E4, SUVR: standardized uptake value ratio, MMSE: mini-mental state exam, PSQI: Pittsburgh sleep quality index, REM: rapid eye movement.

**Table 2.** Age-adjusted correlation between global SUVR and dichotomous variables

Variables	Global SUVR	p-value
Sex		0.794
Male (n=27)	1.280±0.213	
Female (n=49)	1.260±0.225	
ApoE4 genotype		0.049
Carrier (n=14)	1.420±0.315	
Non-carrier (n=62)	1.230±0.178	

SUVR: standardized uptake value ratio, ApoE4: apolipoprotein E4.

**Table 3.** Age-adjusted correlation between global standardized uptake value ratio and continuous variables

Variables	Partial correlation coefficient	p-value
MMSE	0.062	0.597
PSQI	0.056	0.632
Total sleep time (min)	-0.240	0.839
Total time spent in bed (min)	-0.038	0.744
Time spent awake in bed (min)	-0.108	0.357
Number of times awakened during sleep	-0.070	0.551
Total REM sleep time (min)	-0.036	0.76
Total time in light sleep (min)	0.166	0.154
Total time in slow-wave sleep (min)	-0.127	0.277

MMSE: mini-mental state exam, PSQI: Pittsburgh sleep quality index, REM: rapid eye movement, NREM: non-rapid eye movement.

## DISCUSSION

This study investigated the relationship between amyloid positivity and sleep characteristics in the elderly with SCD using a wearable device. The total time in SWS was significantly lower in the amyloid-positive group (39.4±13.1 minutes) compared to the amyloid-negative group (49.5±13.1 minutes) (p=0.009).

Although its exact mechanisms are poorly understood, sleep seems to play a crucial role in amyloid deposition and clearance in the brain. A diurnal fluctuation in ISF A $\beta$  levels was observed in humans and mice, in which increased sleep was associated with decreased amyloid burden.<sup>2</sup> Similar relationships between sleep and amyloid burn were also shown in a study of community-dwelling older adults, where self-reported cases of shorter sleep duration and poorer sleep quality were linked with increased amyloid burden.<sup>16</sup> Both acute and chronic sleep deprivation results in increased amyloid burden, even in healthy adults.<sup>2,17,18</sup>

Sleep is thus a potent modulator of A $\beta$ , both in the short term for monomeric A $\beta$  and in the long term for A $\beta$  deposition and AD pathology progression.<sup>5</sup> Some studies suggest that elevated A $\beta$  aggravates sleep disturbance, suggesting a potentially bidirectional relationship between sleep and AD. In an APP/A $\beta$  overproduction model mice, A $\beta$  accumulation increased time spent awake and decreased NREM and REM sleep time. Deterioration of the sleep-wake cycle and disappearance of diurnal ISF A $\beta$  level fluctuation was also observed with A $\beta$  accumulation; such changes were reversed with the elimination of A $\beta$  deposits in the mice's brains.<sup>5</sup> Despite such mounting evidence, it is still unclear how A $\beta$  induces changes in the sleep architecture.

Recently, the role of SWS in amyloid clearance has been attracting academic attention. A specific association between SWS disruption and increased CSF A $\beta$  levels has been reported.<sup>19</sup> It is already known that patients suffering from AD show sleep disturbance with decreased SWS.<sup>20</sup> Such changes in sleep architecture are also seen in MCI.<sup>21</sup> A study exploring partial sleep deprivation with preserved SWS reported no detectable changes in amyloid burden, which is a curious finding worth further investigation.<sup>22</sup>

There have been numerous attempts at establishing the relationship between SWS and cognitive functions in multiple levels of brain anatomy. Some suggest that the strength of cortical synaptic connections fluctuates during wakefulness and sleep, although the exact properties of such changes, are still unknown.<sup>20</sup> Synchronization of hippocampal sharp wave ripples with thalamic spindle activities during SWS may serve as evidence that memory consolidation is facilitated by SWS.<sup>20</sup> Animal experiments using mice offer deeper insights into changes observed in fluid dynamics in the brain during sleep; interstitial volumes of mice exposed to adrenergic receptor antagonists were significantly greater than those of awake controls but similar to those of asleep or anesthetized mice.<sup>23</sup> The reported increase in the power of slow waves detected by electrocorticography is consistent with the proposed role of SWS in the clearance of toxic metabolites from the brain.<sup>23</sup>

AD is a disease that extends beyond the impairment of an individual's cognitive abilities; its prevalence, effects on the patient's quality of life, and resilience to treatment make it a conspicuous social problem for which primary prevention is deemed the most appropriate and effective strategy yet. While the search for disease-modifying drugs should continue, efforts to repair and maintain a healthy sleep architecture must be implemented to minimize the progression of degenerative changes in AD. Recent efforts against AD have put more emphasis on preemptive control of its risk factors; mounting evidence, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study and updated reviews by Livingston and colleagues, demonstrates the importance of maintaining a healthy, controlled lifestyle in preserving cognitive functions and delaying the onset of the neurodegenerative disease at hand.<sup>23-25</sup> To the best of our knowledge, so far, there is no systematic investigation on the relationship between sleep and AD. As an integral part of everyday human life, it is appropriate to evaluate sleep as an important modifiable risk factor for AD.

Consistent with previous studies, this study showed an association between global SUVR and SWS. However, this study was not without shortcomings, as richer data, with larger sample sizes and longer periods of data collection, should have been gathered. This is especially true in the amyloid-positive group, the size of which was only a fourth of its amyloid-negative counterpart. Accounting for more confounding variables could also have improved the quality of this study. While the inclusion and exclusion criteria helped filter conditions that may affect the subjects' cognitive functions, it was challenging to prevent factors that can affect the subjects' sleep architecture such as the use of hypnotics. For controllable factors such as hypnotics, having a 'washout period' of such medications before enrolling or even excluding subjects using hypnotics altogether would have better tailored the data to the purpose of this study. At the very least, subjects could have been stratified in terms of their hypnotic dependence by identifying the type, dose, and frequency of the hypnotics used.

The use of wearable devices to collect data may have limited the study's quality. The parameters used in this study to quantify sleep characteristics were measured using Fitbit® Alta HR, and some studies have reported no significant differences in measuring time spent in each stage of sleep compared to formal polysomnography.<sup>26</sup> However, other studies have reported that such measurements from Fitbit® may be less accurate when applied to healthy young adults.<sup>27</sup> Compared to wearable devices, polysomnography measurements are more accurate and compatible between institutions. Future studies should have longer periods of data collection with larger populations and standardized tools for evaluating sleep to further elucidate the relationship between slow-wave sleep and amyloid pathology.

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