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Sleep quality and preclinical Alzheimer Disease

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Abstract

Objective—Sleep and circadian problems are very common in Alzheimer Disease (AD). Recent animal studies suggest a bidirectional relationship between sleep and amyloid-β (Aβ), a key molecule involved in AD pathogenesis. This study tested whether Aβ deposition in preclinical AD, prior to the appearance of cognitive impairment, is associated with changes in quality or quantity of sleep.

Methods—Cognitively normal, middle-aged individuals (n=142) had sleep objectively measured using actigraphy for 2 weeks. Concurrent sleep diaries provided nap information. Cerebrospinal fluid Aβ42 levels were used to determine whether amyloid deposition was present or absent. Sleep parameters were assessed with regard to amyloid deposition.

Results—Amyloid deposition was associated with worse sleep quality, specifically worse sleep efficiency (% time in bed that was spent asleep), compared to those without amyloid deposition. In contrast, quantity of sleep was not different between groups, as measured by total sleep time. Frequent napping was associated with amyloid deposition.

Interpretation—Amyloid deposition in the preclinical stage of AD appears to be associated with worse sleep quality, but not with changes in sleep quantity.

Introduction

Sleep-wake problems are common in Alzheimer Disease (AD). Brain regions and pathways important for sleep and wake mechanisms are affected early in AD.[1,2] Sleep-wake abnormalities such as “sundowning”[3] and nocturnal wandering frequently underlie need for institutionalization.[4] In mild-to-moderate AD, sleep-wake disturbances such as increased inadvertent daytime napping and insomnia at night affect 25-40% of AD patients and their caregivers.[5,6] Even in mild cognitive impairment, or very mild dementia, there are abnormalities in sleep architecture and electroencephalography measures.[7] What is not known is whether sleep abnormalities are present in the earliest stages of AD, prior to the manifestation of any cognitive impairment. The pathological changes underlying AD are estimated to begin 10-20 years before any cognitive symptoms appear, with the earliest

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identifiable preclinical stage of AD being the accumulation of amyloid plaques in the brain.[8] Amyloid-β (Aβ) is a 37-43 amino acid peptide produced constantly in the brain in a soluble form. When Aβ aggregates in the brain, it forms insoluble amyloid plaques. Amyloid plaques are a pathological hallmark of AD, and since they sequester soluble Aβ42, a decline in cerebrospinal fluid (CSF) Aβ42 signifies the presence of amyloid plaques.[9–12] Longitudinal studies in sporadic AD as well as dominantly-inherited AD have demonstrated that low Aβ42 precedes cognitive symptoms of AD by 15 years or more.[13,14] In a mouse model of Aβ and amyloid accumulation, sleep-wake cycles became highly fragmented following formation of amyloid plaques.[12] There are no human studies directly assessing the potential association between sleep and AD during the comparable preclinical stage of AD, when amyloid plaques are forming but individuals are cognitively normal.

Several studies suggest that sleep may influence AD pathogenesis. In several cross-sectional studies, insufficient or decreased sleep quality was associated with poor cognitive function.[15–17] Obstructive sleep apnea, a common sleep disorder that causes sleep disruption and hypoxia, increased prospective risk of dementia in a cohort of elderly women.[18] In mouse models of AD, chronic sleep deprivation augmented amyloid plaque formation, while increasing sleep with an orexin receptor antagonist decreased amyloid plaques.[19] In both humans and mouse models, Aβ increases during wakefulness and decreases during sleep.[20] Therefore, sleep abnormalities may increase soluble Aβ levels over the long term, leading to increased chance of amyloid plaque accumulation, further sleep disruption, and subsequently, symptomatic AD (sAD).

We hypothesized that sleep abnormalities would be associated with the presence of amyloid deposition in the preclinical stage of AD. In this study, we specifically hypothesized that changes in sleep quality, sleep quantity, or both, are associated with amyloid deposition.

Participants and Methods

Participants

All participants were cognitively normal research volunteers in longitudinal studies of memory and aging at the Washington University Knight Alzheimer Disease Research Center (ADRC). The majority (124 of 142) were recruited from the Adult Children Study, in which all were age 45-75 years at baseline and 50% have a parental history of sAD. The rest were recruited from a community volunteer cohort enrolled in longitudinal studies of healthy aging and dementia through the Washington University ADRC in which all were age >60 years and healthy at baseline.

All procedures were approved by the Washington University Human Research Protection Office. All participants provided written informed consent. Inclusion criteria included age ≥45 years, CSF obtained within 3 years of actigraphy, and cognitively normal based on a Clinical Dementia Rating (CDR) score of 0. CDR was based on evaluation by experienced clinicians with expertise in dementia, including semi-structured interviews with each participant and a knowledgeable collateral source.[21] The sole exclusion criterion for this study was any neurologic or medical problem causing abnormal (increased or decreased) movement of the non-dominant hand. A total of 145 participants were initially enrolled, however 3 could not be included in analysis due to actigraphy malfunction. Therefore, the final study population included 142 participants.

Sleep measurement

Sleep was measured with an actigraph (Actiwatch2®, Philips Respironics, Bend, OR). Participants were instructed to wear an actigraph on the non-dominant wrist for 14 days, and to push a marker on the actigraph whenever getting in and out of bed. Data were processed

using Actiware™ with wake threshold at the "low" setting of 20, previously shown to correspond best with the gold standard, polysomnography.[22] Details are described in supplemental methods.

Quantity of sleep was measured with total sleep time. Quality of sleep was measured with sleep efficiency, which is total sleep time divided by time in bed, expressed as a percentage. A secondary measure of sleep quality was wake time after sleep onset (WASO).

Concurrently, participants filled out a sleep diary each morning. The sleep diary queried for naps the previous day, bedtime, sleep latency, nighttime awakenings, waketime, and open-ended comment. The number of days per week that at least one nap was taken was calculated as "nap days per week."

CSF Aβ

CSF was obtained by lumbar puncture at 8 am, after overnight fasting, and processed as previously described.[23] Aβ42 was measured by the ADRC Biomarker Core using enzyme-linked immunosorbant assay (INNOTEST; Innogenetics, Ghent, Belgium). A cut-off of 500 pg/mL was used, with values *below* 500 pg/mL indicating strong likelihood for amyloid deposition. This cutoff was based on prior studies indicating this correlated best with amyloid deposition as assessed by Pittsburgh Compound B (PIB).[9,24] Only participants who had CSF obtained within 3 years (before or after) actigraphy measurement were included in analysis.

Other measurements including Sleep History Questionnaire, *APOE* allele, and family history are described in supplemental methods.

Statistical analysis

To compare demographic and sleep variables of those without and with low CSF Aβ42, we used Student's t-tests for normally distributed variables and Mann-Whitney-U tests otherwise. Chi-squared tests were used to compare categorical variables. We used analysis of covariance (ANCOVA) for further analyses to adjust for the effect of covariates such as age and APOEε4 allele. We then performed logistic regression with Aβ42 as the dependent variable, to assess whether certain clinical cutoffs for sleep efficiency, total sleep time, or nap frequency were predictive of amyloid status. Two-sided tests were used. Group differences of 95% confidence interval (CI) not crossing 0, odds ratio 95% CI not crossing 1, and p values of <0.05 were considered significant. All statistical analyses were performed using SPSS® Statistics version 20.0.0. (IBM, Armonk, New York).

Results

This cognitively normal participant population was middle-aged (mean 65.6 ±8.2 years), mostly white, and had a female predominance (Table 1). Thirty-two (22.5%) participants had CSF Aβ42 ≤500 pg/mL, indicating a high likelihood of amyloid deposition.[24] As expected, this group had higher age and a greater proportion with *APOE*ε4 allele, otherwise there were no significant differences in other demographic variables, proportion reporting change in sleep in the past five years, or sleep schedule (bedtime and waketime). Time from CSF Aβ42 measurement to actigraphy measurement was longer in the group with amyloid deposition, however this was not statistically significant. Total sleep time, time in bed, and sleep efficiency were approximately normally distributed, while nap days per week was skewed toward 0 (Figure 1).

To determine whether amyloid deposition is associated with changes in sleep quality or quantity, we compared sleep efficiency and total sleep time between those with low CSF

Aβ42≤500 pg/ml, to those with CSF Aβ42>500 pg/ml (Table 2). Those with low CSF Aβ42 had significantly worse sleep quality, as measured by lower mean sleep efficiency compared to those with normal levels of Aβ42 (80.4% versus 83.7%, t-test p=0.008). After correction for age, gender, and *APOE*ε4 allele carrier status with ANCOVA, the two groups still had a significant difference in sleep efficiency (p=0.038). A secondary measure of sleep quality, WASO, was also significantly worse (higher) in those with low CSF Aβ42 (p =0.045). We performed a subgroup analysis in the subset of participants who reported their sleep had not changed subjectively in the past five years (n = 100), and the difference in sleep efficiency was still significant (p=0.008) between those with and without amyloid deposition, correcting for age, gender, and *APOE*ε4 allele carrier status.

On the other hand, there were no differences between groups in sleep quantity, as measured by total sleep time, with 95% confidence interval of group differences crossing 0 (-16.0 to 19.5 minutes). While there was a trend for longer time in bed for the group with low CSF Aβ42, again this did not reach statistical significance (95% confidence interval of group differences -37.9 to 1.23 minutes).

We assessed naps since frequent napping is another manifestation of sleep-wake disturbance (Table 2). The group with amyloid deposition reported more naps per week in their sleep diaries, however the difference in group averages was not statistically significant (95% CI -1.3 to 0.1 naps per week). When we looked at the proportion of *frequent* nappers, defined as those taking naps on three or more days per week, this was significantly higher in the group with amyloid deposition compared to the group without amyloid deposition (31.2% versus 14.7%, Chi-squared test p=0.034).

Since the direction of the association between sleep and amyloid deposition is unknown, we then used logistic regression with CSF Aβ42 group as the outcome variable, to assess whether sleep parameters could be predictive of amyloid deposition status. For clinically applicable analysis, we used cutoffs of sleep efficiency at 75% and 89%; these are each approximately one standard deviation from the mean, and are clinically meaningful cut-offs for “poor” and “good” sleep efficiency, respectively. The proportion of each group with low CSF Aβ42 shows a clear trend, with worse (<75%) sleep efficiency having the highest proportion with low CSF Aβ42 (Figure 2). This group had an OR of 5.6 of having amyloid deposition compared to the group with best sleep efficiency, however this strong trend did not reach statistical significance (p= 0.055). In contast, sleep quantity, as measured by total sleep time, was not a significant predictor of amyloid deposition.

Discussion

In this study, we found that low CSF Aβ42 is associated with poor sleep efficiency. Since the majority of individuals with low CSF Aβ42 have amyloid deposition as identified by amyloid imaging,[24] this suggests that amyloid deposition in the brain is associated with poor sleep quality, but not sleep quantity. The participants in this study were cognitively normal, therefore any with amyloid deposition would be classified as having a *preclinical* stage of AD. Our findings support the hypothesis that sleep-wake abnormalities are associated with the presence of amyloid deposition in the preclinical stage of AD. Prior studies have identified associations between poor sleep quality and concurrent[15,17] or prospective[25] cognitive test performance. However, this study uses a biological marker of AD, rather than psychometric testing, to define preclinical AD. Since amyloid deposition as assessed by Aβ42 occurs well before decrement in psychometric test performance,[14] our findings may expand the temporal window during which sleep abnormalities are identifiable and potentially modifiable in AD.

Frequent napping was also associated with amyloid deposition. This concurs with a study in an elderly female cohort demonstrating increased napping among individuals with preclinical cognitive decline.[26] However, this is in contrast to a recent study which reported that daytime napping was associated with a lower risk of decline in Mini Mental Status Exam score 10 years later.[27] An important difference in methodology was that we used prospectively collected sleep diary data rather than a one-time question of nap frequency. We found only a moderate correlation between nap frequency as assessed by sleep diary and assessed by a single question ($R^2 = 0.498$, supplemental data). Some of this may be due to inaccurate reporting, either unintentional, or intentional because some individuals may perceive naps to be embarrassing. Additionally, we included inadvertent naps reported in sleep diaries. Inadvertent naps in particular represent an intrusion of sleep into wakefulness, and are symptomatic of poor or insufficient night-time sleep, weakened wake mechanisms, and/or circadian dys-synchrony. We would anticipate that as AD pathology progresses, especially with the development of tauopathy and neurodegeneration, naps become even more frequent, with multiple naps per day. However, we were not able to assess this in our cognitively normal study population, in which taking multiple naps per day was exceedingly rare. Further studies, especially longitudinal as well as from epidemiologically based samples, will be required to better understand these findings in relation to the different stages of preclinical AD.

In contrast to prior studies that reported a U-shaped association between sleep time and cognitive decline,[16,17] we did not find an association between quantity of sleep and amyloid deposition. However, there was a trend toward increased time in bed in those with amyloid deposition. One possible explanation may be that individuals with poor sleep efficiency may increase their time in bed to compensate and obtain approximately the same amount of total sleep time. Support for this comes from a large study which assessed sleep duration by questionnaires and found that an increase in self-reported sleep duration over time was associated with two-fold increased risk of cognitive impairment.[28]

Amyloid deposition may cause sleep-wake fragmentation through several mechanisms. Aβ aggregation may be directly interfering with neuronal function in brain regions key to sleep and wake promotion.[1] In studies of APPswe/PS1δE9 mice which all develop amyloid plaques, sleep-wake cycles and Aβ diurnal variation became abnormal following the onset of amyloid deposition.[12] More specifically, there was more wakefulness during the light phase (when mice typically sleep), and more sleep during the dark phase (when mice are typically awake). When amyloid plaques were eliminated using active immunization with Aβ42, sleep-wake cycles returned to normal. These data strongly support a direct causal role of amyloid deposition in disrupting sleep-wake mechanisms. In longitudinal human studies, preclinical cognitive decline is associated with worsening in sleep quality.[26] Additionally, there are indirect factors that can perpetuate disrupted sleep-wake in AD and aging. Obstructive sleep apnea is common in AD,[29,30] and obstructive respiratory events cause recurrent arousals and awakenings. Preclinical amyloid deposition is associated with decreased physical activity,[31,32] and since exercise deepens sleep, lack of physical activity may lead to worse sleep quality. Depression, a frequent and early symptom of dementia,[33] often manifests in insomnia. Retirement from work, whether precipitated by subtle cognitive changes or not, may contribute to irregular activity and sleep patterns. In later stages of dementia, insufficient exposure to light and activity, particularly in institutional settings, is associated with further deterioration in circadian rhythms, and therefore, sleep-wake patterns.[34]

Moreover, there are mechanisms by which poor sleep may contribute to amyloid deposition. Soluble Aβ is released during physiological synaptic activity.[35] During wakefulness, there is increased neuronal activity and a corresponding increase in Aβ. During sleep, neuronal

activity decreases, as does Aβ. This diurnal variation in soluble Aβ has been documented in several studies in mice as well as in humans, and is attributable to sleep-wake states, though some contribution of circadian factors has not been entirely excluded.[19,20] Brain regions with highest soluble Aβ levels are also those most prone to amyloid plaques.[36] Notably, the brain regions in the default mode network[37] are those that demonstrate the most activity during quiet wakefulness, and are the same areas with the most amyloid deposition during the development of AD pathology.[38] Based on these data, a plausible mechanism would be that chronically insufficient sleep leads to relatively increased neuronal activity, and therefore a relative excess of soluble Aβ. Over time, higher soluble Aβ levels would increase risk of accumulation into aggregated forms of soluble and insoluble Aβ plaques, particularly in those brain regions with the highest activity levels. Indeed, prospective studies have identified poor sleep quality as a risk factor for cognitive decline.[25]

We hypothesize that Aβ accumulation negatively affects sleep-wake behaviors, and conversely, poor sleep may increase risk of Aβ aggregation. Figure 3 illustrates this positive feedback loop, as well as associated factors that influence this relationship. For instance, obstructive sleep apnea may increase Aβ deposition through effects on hypoxic stress and inflammation, or by increasing Aβ levels via increased wakefulness. Cognitive and physical activity levels have a bidirectional relationship with both sleep-wake patterns and AD, and thereby may intensify the feedback loop between poor sleep and AD.

This study has several strengths, including a reasonably large and well-characterized cohort, assessment of AD pathology with a biomarker rather than psychometric testing, and objective measurement of sleep. The cohort was carefully evaluated by experienced clinical researchers and determined to be cognitively normal. Since the study group was fairly young and spans a wide age range, we were able to control for sleep-wake changes related to normal aging. Our measurement of sleep by actigraphy provided objective data that is impossible to obtain by subjective report. There also are some limitations in this study. One is that we did not assess for associations between sleep other markers of amyloid deposition such as amyloid imaging. With time, we will obtain information from this cohort to perform this type of analysis. Another limitation is that this is not an epidemiologically ascertained sample. However, these results should motivate similar analysis in such cohorts. Also, this was an exploratory study and therefore was not powered to assess for a wide variety of sleep-related variables for association with amyloid deposition. In future studies, more targeted questions and parameters can be hypothesized from the outset based on the collected information.

Our data provide impetus for important future studies. Longitudinal follow-up with ongoing measurements of amyloid and sleep (as measured by electroencephalography) should enable us to begin to tease apart the details of the abnormalities in sleep that begin to occur with the onset of AD pathology as well as the directionality of the relationship between sleep and amyloid deposition. If sleep disruption increases risk of future AD, then this provides an even stronger motivation to identify and treat individuals with sleep disorders, such as obstructive sleep apnea. Studies of individuals with both amyloid deposition and evidence of neuronal injury such as elevated CSF tau levels—i.e. the Stage 2 of preclinical AD[8]—will shed light on the interaction between sleep and pathological progression in AD. Lastly, sleep measures themselves could be used as markers of brain function, thereby facilitating faster and easier clinical trials of promising treatments in the preclinical and early clinical stages of AD.

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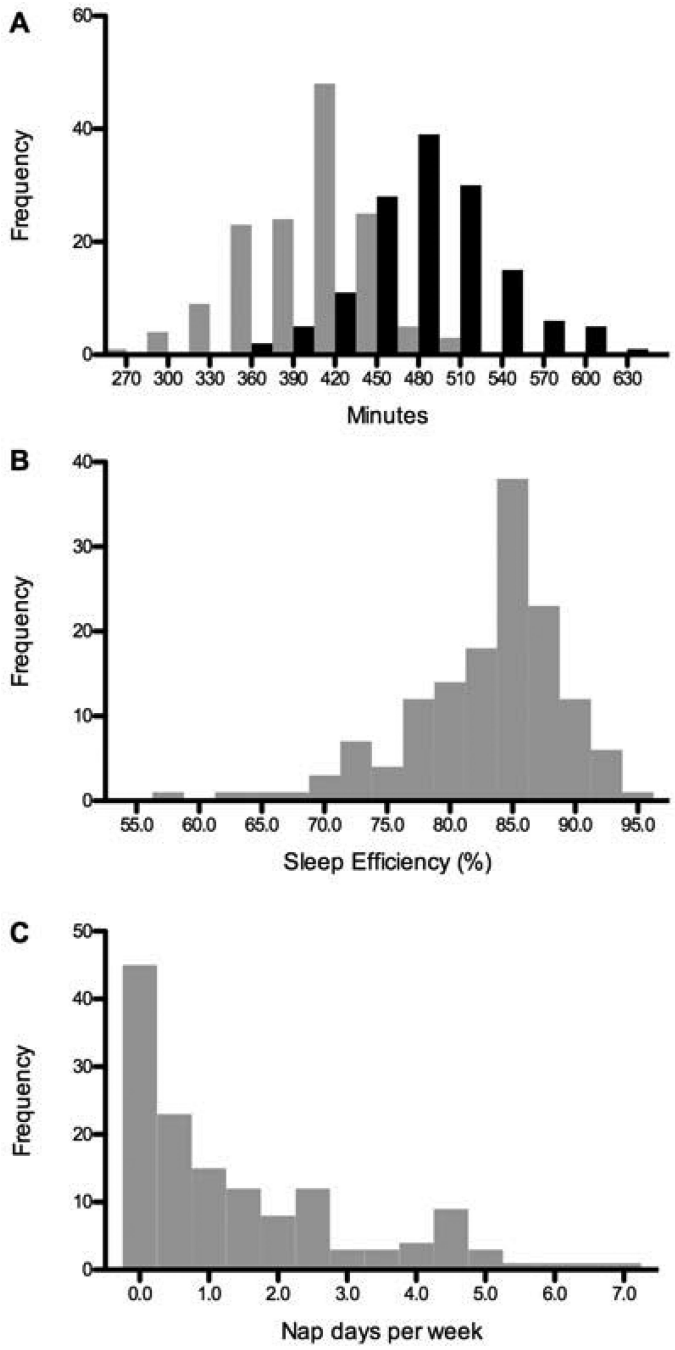

Figure 1. Distribution of sleep and napping parameters

A. Time in bed (black bars) and total sleep time (gray bars) were normally distributed, with mean values 486.4 minutes and 402.6 minutes, respectively. B. Sleep efficiency was also normally distributed, with mean 82.9%. C. Nap days per week was skewed toward zero. Vertical axes represent absolute frequency.

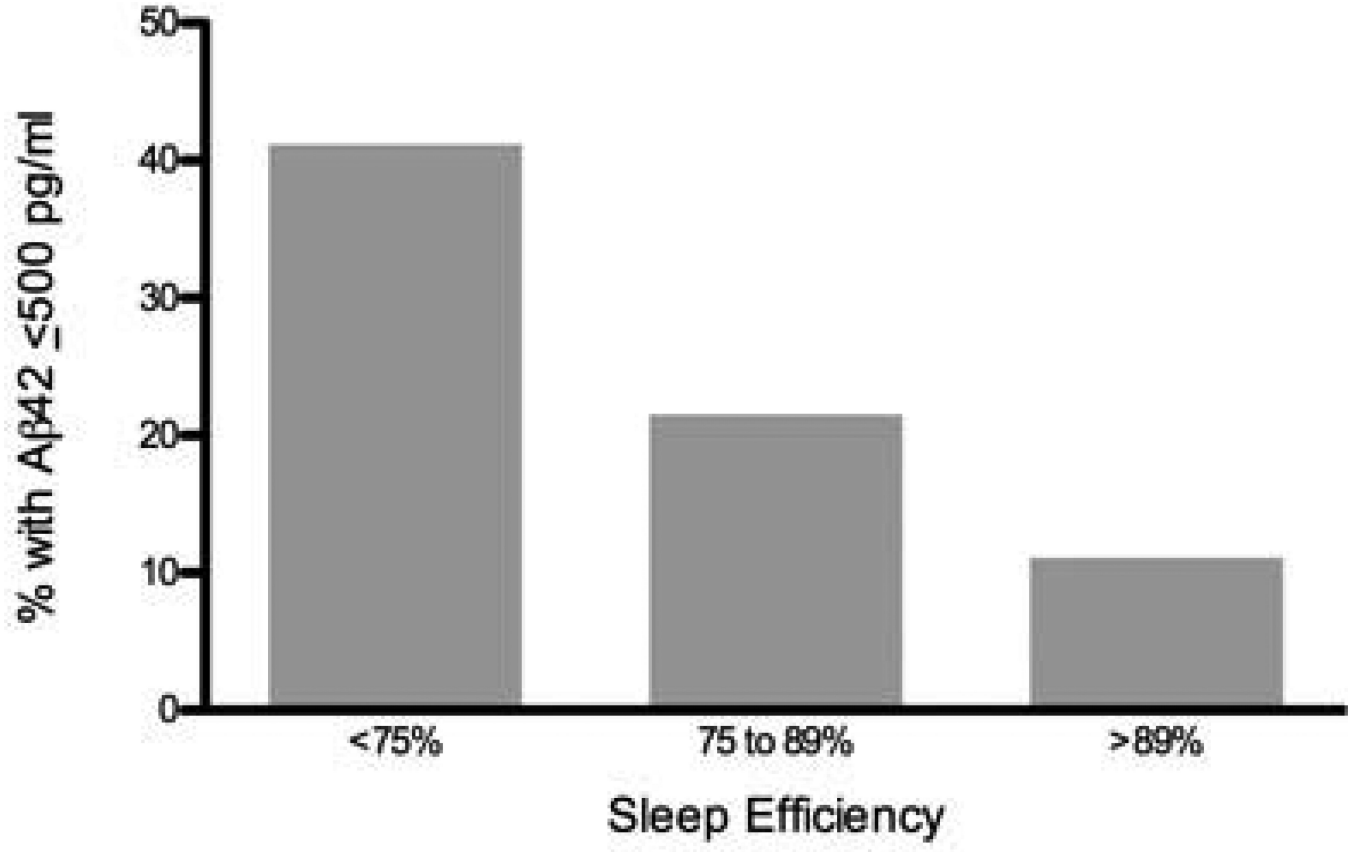

Figure 2. Prevalence of amyloid deposition by sleep efficiency group

Participants were grouped by sleep efficiency, at cutoffs of <75% and >89% for poor and good sleep efficiency, respectively. The proportion in each group with abnormal Aβ42 (≤500 pg/mL) decreases with better sleep efficiency. The group with worst sleep efficiency compared with best sleep efficiency had an OR of 5.6 (0.965 – 32.5) of having amyloid deposition (p 0.055).

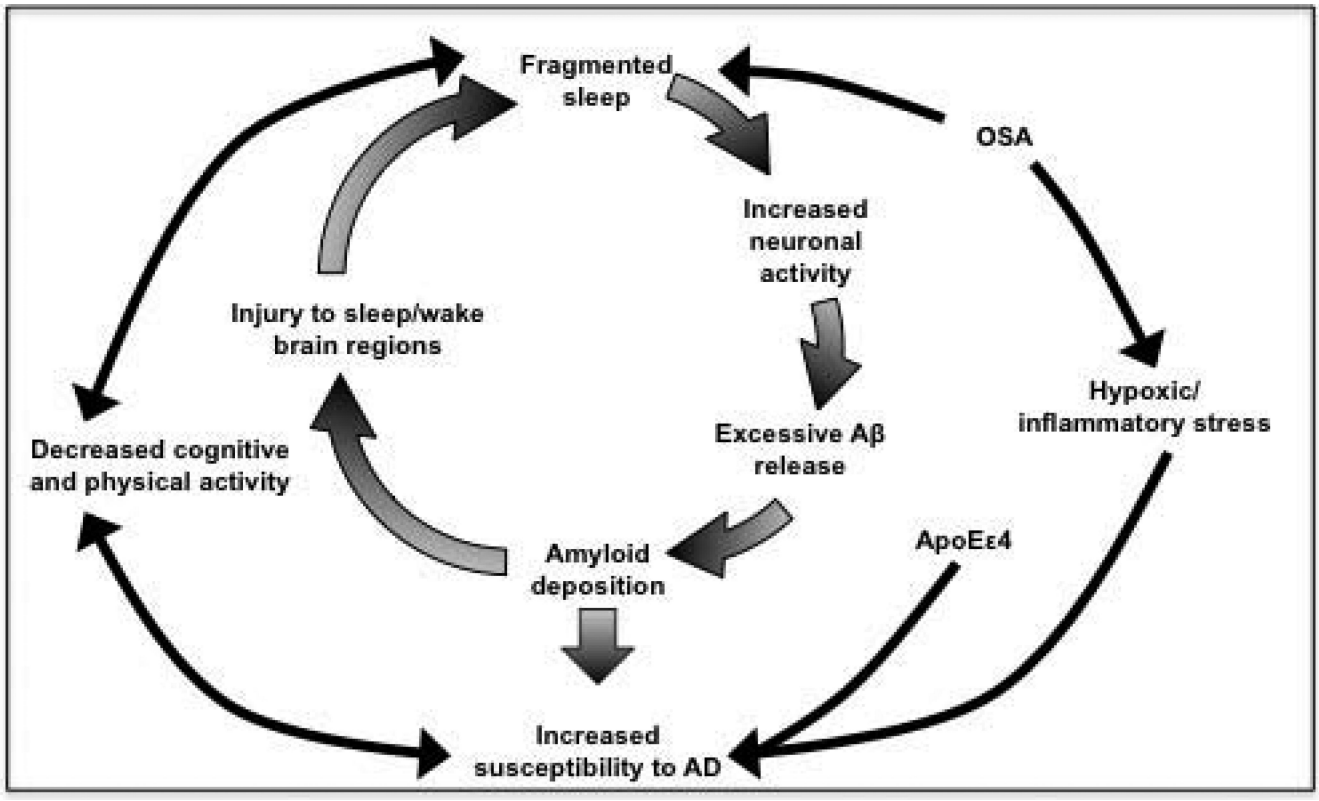

Figure 3. Model of sleep and AD

The inter-relationships and positive feedback loops between sleep, Aβ/amyloid, AD, and related factors are schematized. OSA = obstructive sleep apnea

Table 1

Demographic characteristics

Variable	All N = 142 Number (%)	Aβ42 >500 pg/ml N = 110	Aβ42 ≤500 pg/ml N = 32
Age in years*	Mean 65.6 (SD=8.2)	Mean 64.1 (SD=8.0)	Mean 70.7 (SD=6.3)
45-55 years	19 (13.4%)	19 (17.3%)	0 (0.0%)
55-65 years	46 (32.4%)	39 (35.5%)	7 (21.9%)
65-75 years	59 (41.5%)	42 (38.2%)	17 (53.1%)
>75 years	18 (12.7%)	10 (9.1%)	8 (25.0%)
Female	84 (59.2%)	67 (60.9%)	17 (53.1%)
Race			
Caucasian	133 (93.7%)	103 (93.6%)	30 (93.8%)
African American	8 (5.6%)	6 (5.5%)	2 (6.2%)
Asian	1 (0.7%)	1 (0.9%)	0 (0.0%)
Family history of sAD	74 (52.1%)	57 (51.8%)	17 (53.1%)
*APOE*ε4 allele*	52 (36.6%)	34 (30.9%)	18 (56.2%)
Sleep no reported change in past 5 years	100 (70.4%)	78 (70.9%)	22 (68.8%)
Time from LP to actigraphy in days	499.5 (337.4)	472.3 (SD=342.7)	593.1 (SD=305.5)
Bedtime in clock time	22:57:23 (SD=1:01:23)	23:02:20 (SD=1:03:24)	22:42:34 (SD=0:51:55)
Waketime in clock time	06:55:33 (SD=1:09:46)	06:56:36 (SD=1:09:49)	06:51:57 (SD=1:10:37)

sAD = Symptomatic Alzheimer's Disease

* $p < 0.05$ difference between groups

Table 2

Sleep measures and nap characteristics

Variable	All N = 142	Aβ42 >500 pg/ml N = 110	Aβ42 ≤500 pg/ml N = 32	95% confidence interval of group differences
Sleep Efficiency (%)	82.9 (6.2)	83.7 (5.6)	80.4 (7.7)	(0.8, 5.7)
WASO (minutes)	56.1 (22.6)	54.0 (21.8)	63.1 (23.9)	(-17.9, -0.21)
Total sleep time (minutes)	402.6 (44.6)	403.0 (47.3)	401.3 (49.0)	(-16.0, 19.5)
Time in bed (minutes)	486.4 (49.8)	482.3 (47.3)	500.6 (55.8)	(-37.9, 1.23)
Nap days per week[a]	1.4 (1.7)	1.3 (1.6)	1.9 (1.9)	(-1.3, 0.1)
Frequent Naps ≥3 days per week (number (%))	26 (18.4%)[a]	16 (14.7%)[a]	10 (31.2%)	(-0.32, -0.01)

All data show mean (SD) unless otherwise stated.

[a]One participant was missing sleep diary nap data.