ORIGINAL CONTRIBUTION

Sleep Quality and Preclinical Alzheimer Disease

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Importance: Sleep and circadian problems are very common in Alzheimer disease (AD). Recent animal studies suggest a bidirectional relationship between sleep and β-amyloid (Aβ), a key molecule involved in AD pathogenesis.

Objective: To test whether Aβ deposition in preclinical AD, prior to the appearance of cognitive impairment, is associated with changes in quality or quantity of sleep.

Design: Cross-sectional study conducted from October 2010 to June 2012.

Setting: General community volunteers at the Washington University Knight Alzheimer's Disease Research Center.

Participants: Cognitively normal individuals (n=145) 45 years and older were recruited from longitudinal studies of memory and aging at the Washington University Knight Alzheimer's Disease Research Center. Valid actigraphy data were recorded in 142. The majority (124 of 142) were recruited from the Adult Children Study, in which all were aged 45 to 75 years at baseline and 50% have a parental history of late-onset AD. The rest were recruited from a community volunteer cohort in which all were older than 60 years and healthy at baseline.

Main Outcome Measures: Sleep was objectively measured using actigraphy for 2 weeks. Sleep efficiency, which is the percentage of time in bed spent asleep, was the primary measure of sleep quality. Total sleep time was the primary measure of sleep quantity. Cerebrospinal fluid Aβ42 levels were used to determine whether amyloid deposition was present or absent. Concurrent sleep diaries provided nap information.

Results: Amyloid deposition, as assessed by Aβ42 levels, was present in 32 participants (22.5%). This group had worse sleep quality, as measured by sleep efficiency (80.4% vs 83.7%), compared with those without amyloid deposition, after correction for age, sex, and *APOE*ε4 allele carrier status ($P=.04$). In contrast, quantity of sleep was not significantly different between groups, as measured by total sleep time. Frequent napping, 3 or more days per week, was associated with amyloid deposition (31.2% vs 14.7%; $P=.03$).

Conclusions and Relevance: Amyloid deposition in the preclinical stage of AD appears to be associated with worse sleep quality but not with changes in sleep quantity.

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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 the need for institutionalization.[4] In mild to moderate AD, sleep-wake disturbances such as increased inadvertent daytime napping and insomnia at night affect 25% to 40% of patients with AD 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 to 20 years before any cognitive symptoms appear, with the earliest identifiable preclinical stage of AD being the accumulation of amyloid plaques in the brain.[8] β-Amyloid (Aβ) is a 37– to 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

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dominantly inherited AD, have demonstrated that low Aβ42 levels precede 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] To our knowledge, 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 the 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 an increased chance of amyloid plaque accumulation, further sleep disruption, and, subsequently, symptomatic AD.

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.

METHODS

PARTICIPANTS

All participants were cognitively normal research volunteers in longitudinal studies of memory and aging at the Washington University Knight Alzheimer's Disease Research Center. The majority (124 of 142) were recruited from the Adult Children Study, in which all were aged 45 to 75 years at baseline and 50% have a parental history of symptomatic AD. The rest were recruited from a community volunteer cohort enrolled in longitudinal studies of healthy aging and dementia through the Washington University Alzheimer's Disease Research Center in which all were older than 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 or older, CSF obtained within 3 years of actigraphy, and being cognitively normal based on a Clinical Dementia Rating score of 0. The Clinical Dementia Rating was based on evaluation by experienced clinicians with expertise in dementia, including semistructured 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 nondominant hand. A total of 145 participants were initially enrolled; however, 3 could not be included in analysis because of actigraphy malfunction. Therefore, the final study population included 142 participants.

SLEEP MEASUREMENT

Sleep was measured with an actigraph (Actiwatch 2; Philips Respironics). Participants were instructed to wear an actigraph on the nondominant 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 the wake threshold at the "low" setting of 20, previously shown to correspond best with the gold standard, polysomnography.[22] Details are described in the eAppendix (http://www.jamaneuro.com).

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.

Concurrently, participants filled out a sleep diary each morning. The sleep diary queried for naps the previous day, bedtime, sleep latency, nighttime awakenings, wake time, and open-ended comment. The number of days per week that at least 1 nap was taken was calculated as "nap days per week."

CSF Aβ

Cerebrospinal fluid was obtained by lumbar puncture at 8 AM, after overnight fasting, and processed as previously described.[23] Aβ42 was measured by the Alzheimer's Disease Research Center Biomarker Core using enzyme-linked immunosorbent assay (INNOTEST; Innogenetics). A cutoff of 500 pg/mL was used, with values less than 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.[9,24] Only participants who had CSF obtained within 3 years (before or after) of actigraphy measurement were included in analysis. Other measurements including Sleep History Questionnaire, *APOE* allele, and family history are described in the eAppendix.

STATISTICAL ANALYSES

To compare demographic and sleep variables of those without and with low CSF Aβ42 levels, we used *t* tests for normally distributed continuous variables and Mann-Whitney *U* tests for nonnormally distributed continous variables; χ^2 tests were used to compare categorical variables. We used analysis of covariance for further analyses to adjust for the effect of covariates such as age and *APOE*ε4 allele. We then performed logistic regression with Aβ42 level 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 with a 95% confidence interval not crossing zero, odds ratio and 95% confidence interval not crossing 1, and *P* values of $<.05$ were considered significant. All statistical analyses were performed using SPSS Statistics version 20.0.0 (IBM SPSS).

RESULTS

This cognitively normal participant population was middle-aged (mean [SD] age, 65.6 [8.2] years), was mostly white, and had a female predominance (**Table 1**). Thirty-two participants (22.5%) had a CSF Aβ42 level of 500 pg/mL or less, indicating a high likelihood of amyloid deposition.[24] As expected, this group was older and had a greater proportion with the *APOE*ε4 allele; otherwise, there were no significant differences in other demographic variables, proportion reporting change in sleep in the past 5

Table 1. Demographic Characteristics

Variable	No. (%)		
	All (n = 142)	Aβ42 Level >500 pg/mL (n = 110)	Aβ42 Level ≤500 pg/mL (n = 32)
Age, y, mean (SD)[a]	65.6 (8.2)	64.1 (8.0)	70.7 (6.3)
45-55	19 (13.4)	19 (17.3)	0
56-65	46 (32.4)	39 (35.5)	7 (21.9)
66-75	59 (41.5)	42 (38.2)	17 (53.1)
>75	18 (12.7)	10 (9.1)	8 (25.0)
Female	84 (59.2)	67 (60.9)	17 (53.1)
Race			
White	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
Family history of sAD	74 (52.1)	57 (51.8)	17 (53.1)
*APOE*ε4 allele[a]	52 (36.6)	34 (30.9)	18 (56.2)
Sleep, no reported change in past 5 y	100 (70.4)	78 (70.9)	22 (68.8)
Time from LP to actigraphy, d, mean (SD)	499.5 (337.4)	472.3 (342.7)	593.1 (305.5)
Bedtime, 24-h clock time, mean (SD)	22:57:23 (1:01:23)	23:02:20 (1:03:24)	22:42:34 (0:51:55)
Wake time, 24-h clock time, mean (SD)	06:55:33 (1:09:46)	06:56:36 (1:09:49)	06:51:57 (1:10:37)

Abbreviations: Aβ42, β-amyloid 42; LP, lumbar puncture; sAD, symptomatic Alzheimer disease.
[a] $P < .05$ difference between groups.

years, or sleep schedule (bedtime and wake time). 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 zero (**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 a low CSF Aβ42 level (≤500 pg/mL) with those with a CSF Aβ42 level more than 500 pg/mL (**Table 2**). Those with a low CSF Aβ42 level had significantly worse sleep quality, as measured by lower mean sleep efficiency, compared with those with normal levels of Aβ42 (80.4% vs 83.7%; *t* test $P = .008$). After correction for age, sex, and *APOE*ε4 allele carrier status with analysis of covariance, the 2 groups still had a significant difference in sleep efficiency ($P = .04$). A secondary measure of sleep quality, wake time after sleep onset, was also significantly worse (higher) in those with a low CSF Aβ42 level ($P = .045$). We performed a subgroup analysis in the subset of participants who reported their sleep had not changed subjectively in the past 5 years (n = 100), and the difference in sleep efficiency was still significant ($P = .008$) between those with and without amyloid deposition, correcting for age, sex, 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 a 95% confidence interval of group differences crossing zero (−16.0 to 19.5 minutes). While there was a trend for longer time in bed for the group with a low CSF Aβ42 level, again this did not reach statistical significance (95% CI 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 3 or more days per week, this was significantly higher in the group with amyloid deposition compared with the group without amyloid deposition (31.2% vs 14.7%; χ^2 test $P = .03$).

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 1 SD from the mean and are clinically meaningful cutoffs for "poor" and "good" sleep efficiency, respectively. The proportion of each group with a low CSF Aβ42 level shows a clear trend, with worse (<75%) sleep efficiency having the highest proportion with a low CSF Aβ42 level (**Figure 2**). This group had an odds ratio of 5.6 of having amyloid deposition compared with the group with the best sleep efficiency; however, this strong trend did not reach statistical significance ($P = .06$). In contrast, sleep quantity, as measured by total sleep time, was not a significant predictor of amyloid deposition.

COMMENT

In this study, we found that a low CSF Aβ42 level is associated with poor sleep efficiency. Since the majority of individuals with a low CSF Aβ42 level 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,

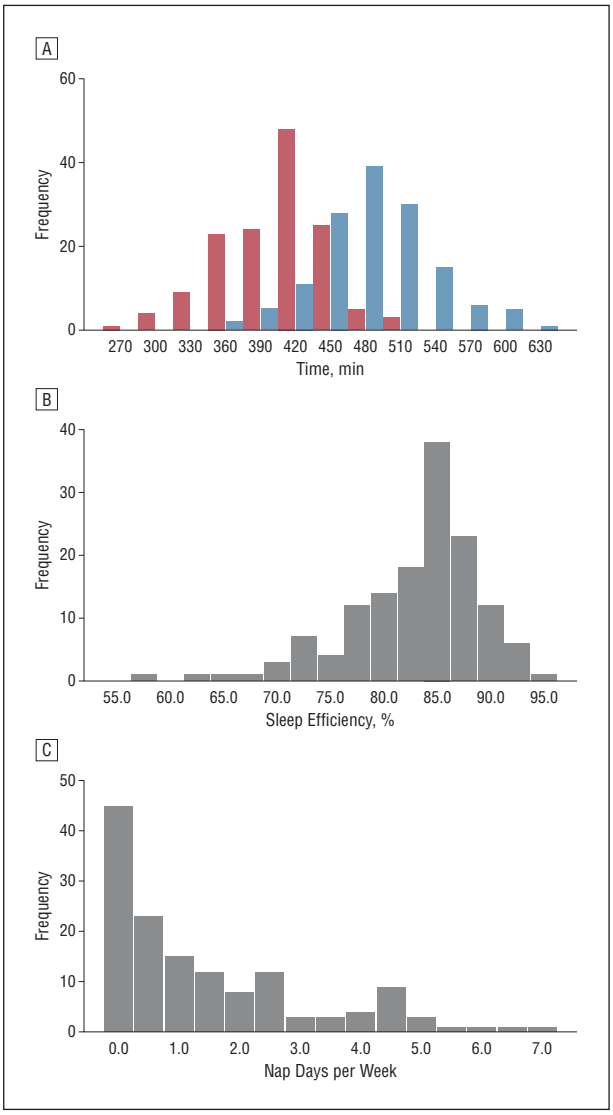

Figure 1. Distribution of sleep and napping parameters. A, Time in bed (blue bars) and total sleep time (red bars) were normally distributed, with mean values of 486.4 minutes and 402.6 minutes, respectively. B, Sleep efficiency was also normally distributed, with a mean value of 82.9%. C, Nap days per week was skewed toward zero. Vertical axes represent absolute frequency.

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 level 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 that reported that daytime napping was associated with a lower risk of decline in Mini-Mental State Examination score 10 years later.[27] An important difference in methods was that we used prospectively collected sleep diary data rather than a 1-time question of nap frequency. We found only a moderate correlation between nap frequency as assessed by sleep diary and a single question ($R^2 = 0.498$) (eAppendix). 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 nighttime sleep, weakened wake mechanisms, and/or circadian dyssynchrony. 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 that assessed sleep duration by questionnaires and found that an increase in self-reported sleep duration over time was associated with a 2-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 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

Table 2. Sleep Measures and Nap Characteristics

Variable	Mean (SD) All (n = 142)	Mean (SD) Aβ42 Level >500 pg/mL (n = 110)	Mean (SD) Aβ42 Level ≤500 pg/mL (n = 32)	95% CI of Group Differences
Sleep efficiency, %	82.9 (6.2)	83.7 (5.6)	80.4 (7.7)	0.8 to 5.7
Wake time after sleep onset, min	56.1 (22.6)	54.0 (21.8)	63.1 (23.9)	−17.9 to −0.21
Total sleep time, min	402.6 (44.6)	403.0 (47.3)	401.3 (49.0)	−16.0 to 19.5
Time in bed, min	486.4 (49.8)	482.3 (47.3)	500.6 (55.8)	−37.9 to 1.23
Nap days per week[a]	1.4 (1.7)	1.3 (1.6)	1.9 (1.9)	−1.3 to 0.1
Frequent naps (≥3 d per week), No. (%)	26 (18.4)[a]	16 (14.7)[a]	10 (31.2)	−0.32 to −0.01

Abbreviation: Aβ42, β-amyloid 42.
[a]One participant was missing sleep diary nap data.

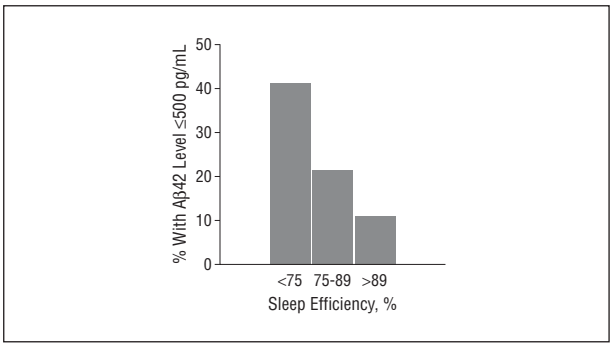

Figure 2. Prevalence of amyloid deposition by sleep efficiency group. Participants were grouped by sleep efficiency, at cutoffs of less than 75% and more than 89% for poor and good sleep efficiency, respectively. The proportion in each group with abnormal β-amyloid 42 (Aβ42) level (≤500 pg/mL) decreases with better sleep efficiency. The group with worst sleep efficiency compared with best sleep efficiency had an odds ratio of 5.6 (95% CI, 0.965-32.5) of having amyloid deposition ($P = .06$).

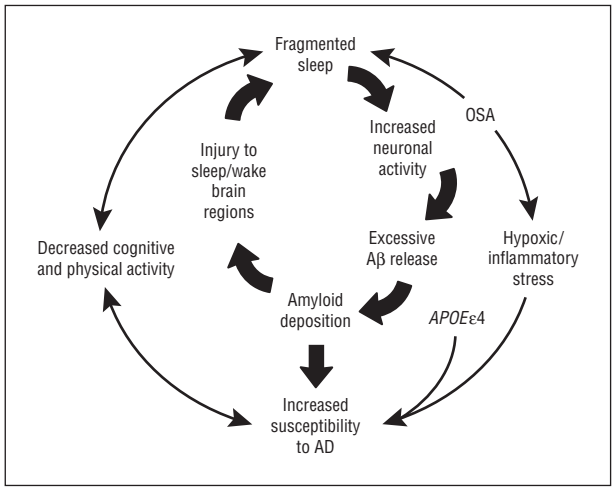

Figure 3. Model of sleep and Alzheimer disease (AD). The interrelationships and positive feedback loops between sleep, β-amyloid (Aβ)/amyloid, AD, and related factors are schematized. OSA indicates obstructive sleep apnea.

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 the 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 are impossible to obtain by subjective report. There also are some limita-

tions in this study. One is that we did not assess for associations between sleep and 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—ie, 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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Online-Only Material: The eAppendix is available at http://www.jamaneuro.com. Listen to an author interview about this article, and others, at http://bit.ly/MT7xg4.
Additional Contributions: Alison Goate, DPhil, director of the Charles F. and Joanne Knight Alzheimer's Disease Research Center Genetics Core, performed *APOE* genotyping.

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