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ORIGINAL ARTICLE

Excessive daytime sleepiness and napping in cognitively normal adults: associations with subsequent amyloid deposition measured by PiB PET

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Abstract

Study Objectives: To determine the association of excessive daytime sleepiness (EDS) and napping with subsequent brain β-amyloid (Aβ) deposition in cognitively normal persons.

Methods: We studied 124 community-dwelling participants in the Baltimore Longitudinal Study of Aging Neuroimaging Substudy who completed self-report measures of EDS and napping at our study baseline and underwent [^{11}C] Pittsburgh compound B positron emission tomography (PiB PET) scans of the brain, an average ±standard deviation of 15.7 ± 3.4 years later (range 6.9 to 24.6). Scans with a cortical distribution volume ratio of >1.06 were considered Aβ-positive.

Results: Participants were aged 60.1 ± 9.8 years (range 36.2 to 82.7) at study baseline; 24.4% had EDS and 28.5% napped. In unadjusted analyses, compared with participants without EDS, those with EDS had more than 3 times the odds of being Aβ+ at follow-up (odds ratio [OR] = 3.37, 95% confidence interval [CI]: 1.44, 7.90, $p = 0.005$), and 2.75 times the odds after adjustment for age, age^2, sex, education, and body mass index (OR = 2.75, 95% CI: 1.09, 6.95, $p = 0.033$). There was a trend-level unadjusted association between napping and Aβ status (OR = 2.01, 95% CI: 0.90, 4.50, $p = 0.091$) that became nonsignificant after adjustment (OR = 1.86, 95% CI: 0.73, 4.75, $p = 0.194$).

Conclusions: EDS is associated with more than 2.5 times the odds of Aβ deposition an average of 15.7 years later. If common EDS causes (e.g., sleep-disordered breathing, insufficient sleep) are associated with temporally distal AD biomarkers, this could have important implications for AD prevention.

Statement of Significance

Both excessive daytime sleepiness (EDS) and napping are common among older adults. Although mounting evidence links sleep disturbance to Alzheimer's disease (AD), little is known about associations of EDS and napping with measures of in vivo β-amyloid (Aβ) deposition. Moreover, the temporal separation of EDS or napping from Aβ measurement has been relatively small in prior studies. To better understand EDS and napping as markers of subsequent AD risk, we studied the link of self-reported EDS and napping with a neuroimaging measure of Aβ deposition taken more than 15 years later on average in community-dwelling adults.

Key Words: aging; biomarkers; brain imaging; epidemiology; neurological disorders; sleepiness; napping

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Introduction

Disturbed sleep has emerged as a candidate risk factor for Alzheimer's disease (AD). Multiple studies link indices of poor sleep to cognitive impairment and decline [1], and more recent studies link sleep disturbance to AD biomarkers. We showed in the Baltimore Longitudinal Study of Aging (BLSA) that reports of shorter sleep duration and poorer sleep quality were associated with greater β-amyloid (Aβ) deposition measured by positron emission tomography (PET) scans, an average of less than 2 years later [2]. Another study linked poorer actigraphic sleep efficiency and greater sleep fragmentation, and reports of frequent napping, with cerebrospinal fluid (CSF) measures of Aβ deposition [3]. Recently, a single night of total sleep deprivation increased PET measures of Aβ in a study of healthy humans [4], although in another study, partial sleep deprivation over five nights produced no measurable effect on CSF-derived AD biomarkers [5]. Furthermore, numerous studies link sleep-disordered breathing (SDB) to poor cognitive outcomes, and recent studies tie SDB to AD biomarkers [6, 7].

Excessive daytime sleepiness (EDS) is common among older people. Commonly a manifestation of SDB, EDS can also result from medication side effects and interactions, mood disorders, narcolepsy, insufficient sleep, and circadian rhythm alterations [8–12]. Like SDB, EDS has been tied to poor cognitive outcomes and identified as a possible marker of AD [13–16]. Reports of greater sleepiness on the Medical Outcomes Study (MOS) Sleep Scale [17] were recently linked to greater Aβ deposition in several brain regions on [^{11}C] Pittsburgh compound B (PiB) PET scans [18], although this association was not replicated using CSF Aβ measures [19]. In addition, a 2018 study tied reports of EDS on the Epworth Sleepiness Scale [20] to subsequent increases in Aβ burden within particular brain regions [21].

Napping is a common behavior among older people and has been linked to both benefits to and decrements in cognitive performance [22–27]. Much less is known about the association of napping and Aβ deposition, although studies have reported associations of self-reported napping with greater amyloid burden measured by CSF [3] and PiB PET scans [18].

Whereas prior studies have measured EDS or napping in temporal proximity to measures of amyloid burden (i.e. an average of less than 1.5 years apart) [3, 18, 19] or assessed EDS-related change in Aβ burden over a brief period (i.e. an average of 2.2 years) [21], little is known about their association with temporally distal measures of AD pathology. We investigated the association of self-reported EDS and napping with Aβ deposition, an average of 15.7 years later in community-dwelling older adults.

Methods

Participants

We studied Baltimore Longitudinal Study of Aging Neuroimaging Study (BLSA-NI) participants. The BLSA is an ongoing continuous enrollment cohort study that began in 1958 [28]. Prospective participants for the BLSA must be very healthy on enrollment; they are ineligible if they have any medical conditions other than controlled hypertension, any mobility limitations, cognitive impairment, physical disability, or health conditions that lead to functional impairment or diminished life expectancy, or if they take ongoing medications for chronic pain, antibiotics, corticosteroids, immunosuppressant drugs, or histamine H2 blockers.

BLSA participants are only eligible for the BLSA-NI if they have no neurological illness, and no significant pulmonary or cardiovascular disease or metastatic cancer at BLSA-NI enrollment. Neuroimaging assessments began in the BLSA on February 10, 1994 and are ongoing. PIB PET scans began on June 9, 2005. We studied 124 BLSA-NI participants with self-report measures of EDS (n = 123; one participant had missing EDS data) or napping (n = 123; a different participant was missing napping data) and PiB PET scan data who were cognitively normal at sleepiness and napping assessment. All participants gave written informed consent to protocols approved by institutional review boards associated with the National Institute on Aging Intramural Research Program and Johns Hopkins University.

Sleepiness and napping

Between 1991 and 2000, BLSA participants were asked "Do you often become drowsy or fall asleep during the daytime when you wish to be awake? (e.g. falling asleep watching TV or reading)." Response options were "yes" and "no." They also were asked, "Do you nap?" with response options of "daily"; "1–2 times/week"; "3–5 times/week"; and "rarely or never." In 2003, the sleepiness item was replaced with a differently worded item with a different range of response options and the napping item was removed. Thus, we focus on sleepiness and napping as measured in the earlier phase of the BLSA.

[^{11}C] PiB PET imaging

Aβ deposition was quantified by PiB PET scan. To reduce head motion and ensure consistent head placement, a thermoplastic face mask was individually fitted and applied to each participant prior to PET scans on a General Electric Advance scanner. Scanning commenced in three-dimensional mode immediately following an intravenous bolus injection of a mean ±SD of approximately 15 millicuries (555 megabecquerels) of PiB: 4 × 0.25, 8 × 0.50, 9 × 1.00, 2 × 3.00, and 10 × 5.00 min (70 min, 33 frames total). The images are reconstructed by filtered back projection using a ramp filter.

Magnetic resonance imaging acquisition

Participants underwent magnetic resonance imaging (MRI) and PiB PET scans at the same visit. Scans were completed with one of the two different sequences and on one of three scanners, depending on year of scanning. A total of 13 participants completed a spoiled gradient-recalled (SPGR) acquisition on a 1.5-T device (Signa; General Electric) (repetition time [TR], 35 ms; echo time [TE], 5 ms; flip angle, 45°; image matrix, 256 × 256; 124 sections; pixel size, 0.94 × 0.94 mm; slice thickness, 1.5 mm). Overall, 111 participants underwent a magnetization-prepared rapid acquisition with gradient echo (MPRAGE); 6 on a 1.5-T scanner (Intera; Philips) (TR, 6.8 ms; TE, 3.3 ms; flip angle, 8°; image matrix, 256 × 256; 124 sections; pixel size, 0.94 × 0.94 mm; slice thickness, 1.5 mm), and 105 on a 3-T device (Achieva; Philips) (TR, 6.8 ms; TE, 3.2 ms; flip angle, 8°; image matrix, 256 × 256; 170 sections; pixel size, 1 × 1 mm; slice thickness, 1.2 mm).

Image processing

For each participant, we aligned the time frames of the PiB PET scan to the mean of the first 2 min to correct for motion [29]. To facilitate registration, a static image was obtained for each participant by averaging the time frames within the first 20 min of the dynamic PET scan, and we rigidly registered the MRI onto the 20 min mean. A diffeomorphic registration approach was used to compute a study-specific template from baseline 3-T MPRAGE images for the whole BLSA PiB sample [30]. We generated 1.5-T MPRAGE and 1.5-T SPGR templates based on the 3-T template with a patch-based image synthesis procedure [31] and used FreeSurfer (version 5.1, http://surfer.nmr.mgh.harvard.edu) to segment the 3-T MPRAGE image template [32]. We registered the corresponding MRI template to each participant's MRI with diffeomorphic registration [33] and transformed the FreeSurfer segmentation onto the PET scans. We calculated distribution volume ratio (DVR) images in native PET space with a simplified reference tissue model; cerebellar gray matter served as the reference region [34].

Our analysis focused on the mean cortical DVR (cDVR), an index of global amyloid deposition, defined as the mean of DVRs for the following cortical regions: frontal, cingulate, lateral temporal, parietal (including the precuneus), and lateral occipital; the sensorimotor strip was excluded. Participants with a cortical DVR of >1.06 were considered Aβ+, based on the results of a two-class Gaussian mixture model for the entire BLSA PiB sample at baseline [35].

Other measures

Demographic data were collected on BLSA enrollment and at each visit. At visits, a nurse practitioner reviewed medical records and completed a detailed health interview regarding signs, symptoms, and diagnoses of medical conditions. Participants were weighed and measured and body mass index was calculated (BMI; kg/m^2). At the same time that they provided data on sleepiness and napping, participants were asked "Do you snore often and loudly?", with response options of "yes" and "no." A neuropsychological battery and the Clinical Dementia Rating (CDR) Scale [36] were administered at each visit for PiB PET participants. Clinical and neuropsychological data were reviewed at a consensus case conference if participants had ≥4 errors on the Blessed Information Concentration Test [37] or a score of ≥0.5 on the CDR. The Petersen criteria were used for mild cognitive impairment (MCI) [38] and Diagnostic and Statistical Manual of Mental Disorders (Third Edition, Revised) criteria were used for dementia diagnosis [39]. Participants provided blood samples and Apolipoprotein E (ApoE) ε4 carrier status was determined [40, 41].

Statistical analysis

We calculated descriptive statistics and compared participant characteristics by responses to EDS and napping measures, using *t*-tests for continuous variables and Fisher exact tests for categorical variables. Based on the distribution of napping frequency in the sample, we defined participants reporting napping rarely or never as non-nappers, and those napping 1–2 times per week or more as nappers (Supplementary Table 1). To determine the association of EDS and napping with subsequent amyloid deposition, we performed unadjusted and multivariable logistic regression analyses with either EDS or napping as the primary predictor and amyloid deposition (Aβ+ vs. Aβ–) as the outcome. Multivariable models were adjusted for age, age^2, sex, education, and BMI. An $\alpha < 0.05$ indicated statistical significance. Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Participants had a mean ± standard deviation age of 60.1 ± 9.8 (range 36.2 to 82.7) years at the time of EDS and sleepiness assessment (i.e. our study baseline; Table 1). PiB imaging occurred 15.7 ± 3.4 (range 6.9 to 24.6) years later (i.e. at follow-up), when participants were aged 75.8 ± 8.2 (range 55.7 to 93.4) years. Overall, 50.8% were women and 21.8% were non-White. They had 16.7 ± 2.2 years of education and a BMI of 26.8 ± 3.7. Approximately 24% had EDS and 29% were nappers. There was no association between EDS and napping (Fisher's exact $p = 0.24$; Supplementary Table 2). A total of 43 participants (34.7%) were Aβ+ on PiB scans. Compared with those without EDS, those with EDS were older, and compared with non-nappers, nappers were older, more likely to be male, and had slightly more education. At the time of PiB imaging, six participants (4.8%) had cognitive impairment based on consensus diagnosis; three had MCI, two had AD dementia, and one was thought to have Lewy Body dementia.

Participants with EDS were more likely to be Aβ+ at follow-up (56.7%) than those without EDS (28.0%; chi-square $p = 0.004$). In unadjusted analyses, participants with EDS had more than three times the odds of being Aβ+ at follow-up, compared to

Table 1. Participant characteristics* (mean ± standard deviation or *n* (%))

	EDS+ *n* = 30 (24.4%)	EDS– *n* = 93 (75.6%)	P	Napping+ *n* = 35 (28.5%)	Napping– *n* = 88 (71.5%)	P
Age at baseline	65.3 ± 9.8	58.5 ± 9.2	<0.001	63.0 ± 10.4	58.8 ± 9.4	0.033
Age at PiB	80.6 ± 7.8	74.4 ± 7.7	<0.001	78.3 ± 7.7	74.7 ± 8.2	0.028
Sleep-PiB interval (yrs)	15.3 ± 3.2	15.9 ± 3.4	0.368	15.3 ± 3.4	15.9 ± 3.3	0.388
Female	13 (43.3)	50 (53.8)	0.40	9 (25.7)	53 (60.2)	<0.001
Non-White	6 (20.0)	20 (21.5)	1.00	5 (14.3)	22 (25.0)	0.234
Education (yrs)	16.2 ± 2.5	16.8 ± 2.1	0.250	17.4 ± 1.7	16.3 ± 2.3	0.017
BMI (kg/m^2)	27.3 ± 3.3	26.6 ± 3.8	0.360	26.9 ± 3.9	26.8 ± 3.6	0.846

N = 124.

*All characteristics from time of sleep assessment except age at PiB and sleep-PiB interval.

BMI = body mass index; PiB = [^{11}C] Pittsburgh compound B positron emission tomography. Continuous variables were compared using *t*-tests and categorical variables with Fisher exact tests.

those without EDS (odds ratio [OR] = 3.37, 95% confidence interval [CI]: 1.44, 7.90, p = 0.005; Table 2). After adjustment for age, age^2, sex, education, and BMI, those with EDS had 2.75 times the odds of being Aβ+ at follow-up, compared to those without (OR = 2.75, 95% CI: 1.09, 6.95, p = 0.033).

Similarly, participants who napped were more likely to be Aβ+ at follow-up (45.7%), compared with non-nappers (29.6%), but this was at the trend level (chi-square p = 0.088). In unadjusted analyses, nappers had double the odds of being Aβ+ at follow-up, also at the trend level (OR = 2.01, 95% CI: 0.90, 4.50, p = 0.091). This effect decreased and was nonsignificant after adjustment (OR = 1.86, 95% CI: 0.73, 4.75, p = 0.194).

We also examined the association between self-report of snoring at baseline (yes vs. no) and subsequent Aβ status. There were no significant associations in unadjusted (OR = 1.26, 95% CI: 0.53, 3.01, p = 0.598) or multivariable-adjusted analyses (OR = 1.13, 95% CI: 0.43, 2.96, p = 0.803).

In a sensitivity analysis adding ApoE ε4 status to the adjusted models with EDS or napping as the primary predictor, the association between EDS and Aβ+ status decreased slightly and became borderline significant (OR = 2.44, 95% CI: 0.91, 6.54, p = 0.076); the association between napping and Aβ+ status remained nonsignificant (OR = 1.73, 95% CI: 0.65, 4.62, p = 0.272).

Discussion

In this study, we found that, among community-dwelling adults with a mean age of 60 years at baseline, those reporting EDS on a simple yes or no item had 2.75 times the odds of being Aβ+ on subsequent PiB PET scans, an average of 15.7 years later, after accounting for potential confounders. When we added ApoE ε4 to the adjusted model, this association decreased to the trend level of significance, but this may be because the ε4 allele promotes EDS or sleep disturbances that cause it (e.g. SDB) [42]. We also observed a trend-level association between napping and subsequent Aβ status in unadjusted analyses. Thus, among cognitively normal older adults, EDS may be an important marker of risk for subsequent Aβ deposition.

Our findings are consistent with a prior study, in which higher scores on the Somnolence composite of the MOS Sleep Scale—which consists of items about daytime drowsiness/ sleepiness, difficulty staying awake, and taking naps—were associated with greater Aβ deposition on PiB PET across numerous brain regions in older adults without dementia [18]. In that study, there was an average of 0.69 ± 0.98 years between sleep assessment and PET scans. A more recent study in cognitively normal persons showed that baseline EDS, measured by the Epworth Sleepiness Scale, was associated with greater subsequent increases in Aβ on PiB PET over an average of 2.2 years [21]. In the present study, sleepiness and napping data collection preceded PET scans by 15.7 ± 3.4 years (minimum = 6.9, maximum = 24.6), indicating that EDS in cognitively normal older adults is associated with amyloid deposition at least 7 years, and perhaps more than a decade or two later. In contrast to other studies [3, 18], we found no significant association between reports of napping and Aβ status.

Our results prompt at least four interpretations. First, EDS at baseline may have resulted directly from disturbed sleep that itself promotes Aβ deposition (Figure 1A). As described above, SDB and shorter or poorer-quality sleep can promote EDS and have been linked to markers of AD pathology [2, 3, 6, 7]. Under this scenario, assessment of EDS could help identify persons at elevated AD risk. This would be important not only for prognosis, but also because treating causes of EDS could help prevent Aβ deposition. Importantly, this interpretation assumes that our participants were free of Aβ at EDS assessment. Although targeting sleep disorders has not yet been shown to reduce AD risk in humans, animal studies demonstrate that sleep deprivation increases Aβ deposition [43, 44], and link hypoxia—an important consequence of SDB—to Aβ production [45–47], providing support for this approach to AD prevention. The normal cognitive status of participants at baseline and the significant temporal separation of baseline EDS and napping measures from Aβ status at follow-up enhance the plausibility of EDS occurring prior to amyloid deposition in our sample. Given the mean age at EDS assessment (60.1 years), a number of our PiB-positive participants were probably PiB-negative at that time. However, we cannot state this definitively without a baseline measure of Aβ.

Although unlikely, given participants' mean age at our study baseline, the second interpretation is that baseline EDS resulted indirectly from Aβ deposition. Indeed, Aβ aggregation has been shown to disrupt sleep/wake patterns in an AD mouse model, and active immunization with Aβ42 prevented both Aβ deposition and sleep/wake disturbance in this model organism [48]. Thus, Aβ deposition may promote EDS by limiting sleep duration or quality (Figure 1B). Furthermore, baseline Aβ burden may have promoted SDB in our sample by affecting respiratory control, resulting in EDS. Although there are elevated rates of SDB in persons with AD, perhaps in part due to Aβ deposition [49], little is known about the effect of preclinical Aβ deposition on respiration during sleep. In persons with EDS resulting from Aβ deposition-related sleep alterations, a clinical sleep evaluation including polysomnography could identify existing specific sleep disturbances. As in the first interpretation, this could have prognostic utility and identify a need for therapies to improve sleep. The current consensus is that a feed-forward system exists in which disturbed sleep increases Aβ deposition, which disturbs sleep, etc. [50]. Although there is not yet evidence that

Table 2. Association of sleep variables with amyloid deposition

	n	n (%) PiB+	Unadjusted OR (95% CI), p value	MV-adjusted* OR (95% CI), p value
EDS +	30	17 (56.7)	3.37 (1.44, 7.90), p = 0.005	2.75 (1.09, 6.95), p = 0.033
EDS–	93	26 (28.0)	1.00 (ref)	1.00 (ref)
Napping +	35	16 (45.7)	2.01 (0.90, 4.50), p = 0.091	1.86 (0.73, 4.75), p = 0.194
Napping–	88	26 (29.6)	1.00 (ref)	1.00 (ref)

Overall N = 124; one participant was missing EDS data and another napping data, yielding n = 123 for each regression model.
*Adjusted for age, age^2, sex, education, body mass index.
CI = confidence interval; EDS = excessive daytime sleepiness; MV = multivariable; OR = odds ratio; PiB+ = [^{11}C] Pittsburgh compound B cortical distribution volume ratio >1.06.

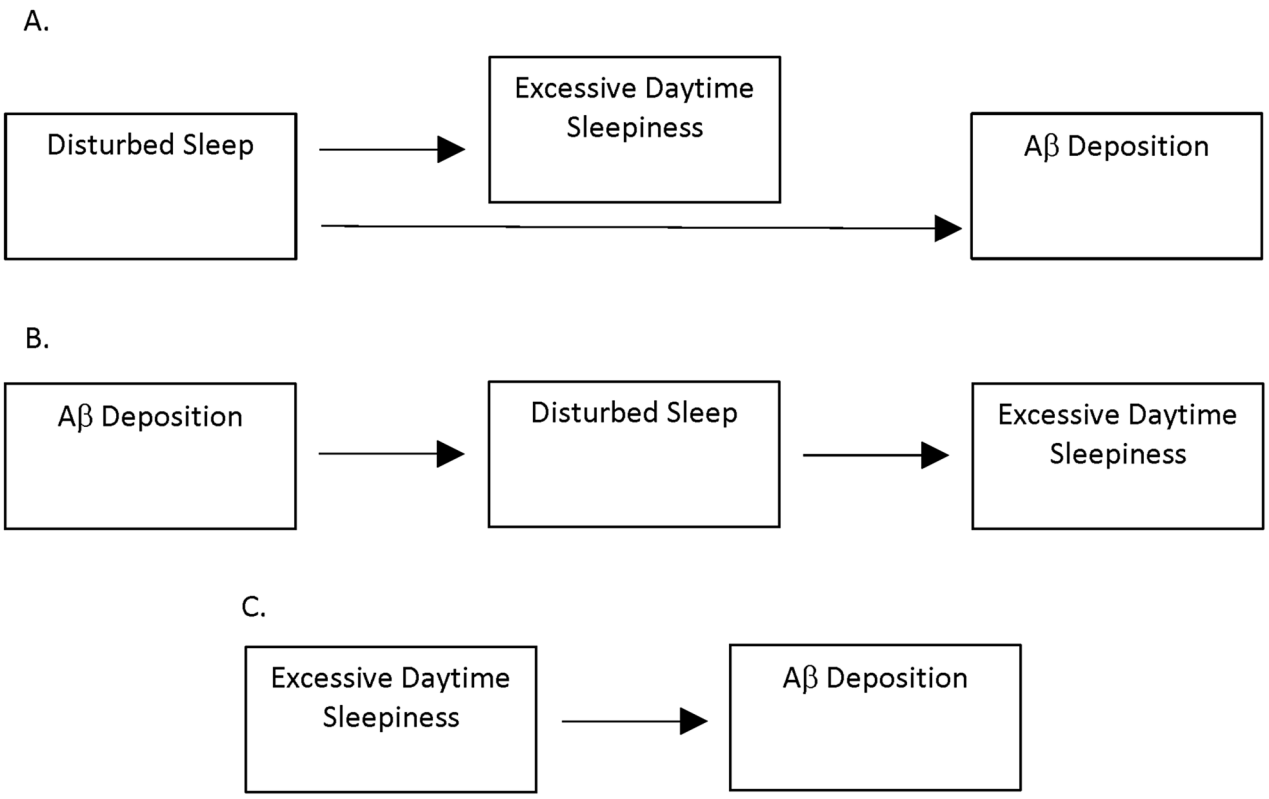

Figure 1. Hypothetical links among disturbed sleep, excessive daytime sleepiness, and Aβ deposition.

interrupting this cycle by treating disturbed sleep resulting from Aβ deposition slows AD progression, this is an important area for investigation.

The third possibility is that, rather than being a marker of risk for Aβ deposition, EDS actually promotes Aβ aggregation (Figure 1C). However, no pathway has been identified by which EDS itself might increase Aβ aggregation, making this a less plausible explanation. The fourth possibility is that alterations in circadian rhythms may have played a role in all of the above scenarios. Circadian rest/activity rhythm alterations have been tied to an increased risk of MCI or dementia diagnosis [51] and preclinical amyloid deposition [52] in humans, and in an AD mouse model, deletion of the *Bmal1* circadian clock gene disturbed Aβ dynamics, increased ApoE expression, and promoted development of Aβ plaques [53]. Because circadian alterations can manifest as sleepiness or napping, changes in circadian rhythms may have driven some of our results. Several other factors, including medications, psychopathology, narcolepsy, and insufficient sleep can result in EDS, as mentioned above. If they are also found to promote Aβ deposition, targeting them directly may help prevent AD in addition to relieving EDS and enhancing daytime function.

This study's primary strengths are its large sample of cognitively normal adults with PiB PET data, and the substantial interval between EDS and napping assessment and subsequent PiB imaging. To the best of our knowledge, this is the first study with these characteristics. Its primary limitations are its observational design and the absence of a baseline Aβ measure, which limit us from drawing firm causal inferences. Another important limitation is that EDS and napping were measured at only one time point, and we did not capture trajectories of sleepiness or napping over the roughly 15 years between measurement of predictors and our outcome. In addition, our napping measure did not capture nap duration, which may affect observed associations. Finally, our assessment of EDS was limited to a single item with a yes/no response format. A validated self-report measure of EDS, such as the Epworth Sleepiness Scale, or an objective measure of sleepiness, such as the multiple sleep latency test, would have been preferable. On the other hand, nondifferential misclassification of exposure (EDS), in which participants are as likely to misclassify themselves regardless of their subsequent disease (Aβ) status, would have biased results toward the null. Because systematic misclassification of EDS status based on Aβ status is unlikely in a cognitively normal sample, the true association between EDS and Aβ deposition is probably stronger than our results indicated. Actigraphy would be helpful to estimate napping (and rest/activity rhythms) in future studies, with sleep diaries to assess whether naps were intentional or, as in EDS, unintentional. Taken together, future observational studies with repeated objective measures of EDS and napping, baseline and follow-up measures of AD biomarkers, and further experimental human and animal research are needed to clarify the nature of the association of EDS and napping with Aβ deposition and related AD biomarkers. Studies that include polysomnography or screen participants for SDB would help identify the role of SDB in the observed associations.

In conclusion, our findings provide further support for the literature on sleep disturbance as a risk factor for AD. They suggest that EDS—a common clinical phenomenon frequently resulting from disturbed sleep—identifies those with more than double the odds of Aβ+ status derived an average of ~16 years later. That EDS was measured with a single yes/no question in

our study demonstrates the ease with which this risk might be assessed in a routine clinical encounter. Screening for EDS could help identify those at elevated AD risk, and further support for a causal role of sleep disturbance would recommend that sleep-related interventions be included in AD prevention efforts.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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