Numerous studies have linked disturbed sleep to cognitive impairment in older adults. Individuals with Alzheimer disease (AD) have been shown to spend more time in bed awake \(^1\) and have more fragmented sleep than those without AD. \(^2,3\) and studies of healthier older adults document associations between worse self-reported sleep and lower cognitive performance. \(^4,5\) In addition, recent research demonstrates that poor sleep quality, measured using wrist actigraphy, is associated with lower cognitive performance in community-dwelling older adults. \(^6\) Although these findings indicate that sleep disturbance is associated with poor cognitive outcomes, whether poor sleep contributes to the neuropathological changes underlying cognitive decline remains unclear.

β-Amyloid (Aβ) plaques are one of the hallmarks of AD, and fluctuations in Aβ peptide levels may be regulated by sleep/wake patterns. Kang et al\(^7\) demonstrated that levels of Aβ in brain interstitial fluid increased with time awake and decreased during sleep in wild-type mice and a mouse model of AD. The authors also demonstrated similar fluctuations in cerebrospinal fluid levels of Aβ in young humans. Sleep deprivation in the AD mouse model produced a substantial increase in Aβ plaque burden. \(^7\) We are unaware of any published studies that have investigated whether sleep disturbance is associated with neuroimaging evidence of Aβ deposition in the brains of older living human participants.

We used data from community-dwelling participants in the Baltimore Longitudinal Study of Aging (BLSA) to investigate whether self-reported sleep variables were associated with fibrillar Aβ burden, measured in vivo with positron emission tomography (PET) with the tracer carbon 11-labeled Pittsburgh compound B positron emission tomography distribution volume ratios (DVRs).

**RESULTS** After adjustment for potential confounders, reports of shorter sleep duration were associated with greater Aβ burden, measured by mean cortical DVR (B = 0.08 [95% CI, 0.03-0.14]; \(P = .005\)) and precuneus DVR (B = 0.11 [0.03-0.18]; \(P = .007\)). Reports of lower sleep quality were associated with greater Aβ burden measured by precuneus DVR (B = 0.08 [0.01-0.15]; \(P = .03\)).

**CONCLUSIONS AND RELEVANCE** Among community-dwelling older adults, reports of shorter sleep duration and poorersleep quality are associated with greater Aβ burden. Additional studies with objective sleep measures are needed to determine whether sleep disturbance causes or accelerates Alzheimer disease.

\(^{1,2,3,4,5,6,7}\)
compound B (PiB). We hypothesized that reports of more fragmented sleep, shorter sleep duration, and poorer sleep quality would be associated with a greater Aβ burden.

Methods

Participants

We studied participants in the BLSA Neuroimaging Study (BLSA-NI), a substudy of the larger BLSA.9 On enrollment, BLSA participants were required to be free of cognitive impairment, mobility limitations, physical disability, major diseases (other than controlled hypertension), and conditions that can negatively affect functioning or life expectancy or that require ongoing antibiotic, immunosuppressant, corticosteroid, chronic pain medication, or histamine, blocker therapy. At study visits, participants spent more than 48 consecutive hours at the BLSA Clinical Laboratory, where they underwent height and weight measurement and a medical examination, completed multiple questionnaires and measures of cognition and physical function, and provided blood and urine samples for assays.

The BLSA participants were eligible for the BLSA-NI if they were free of neurological disease, significant cardiovascular and pulmonary disease, and metastatic cancer at the BLSA-NI baseline. Neuroimaging studies of BLSA participants began February 10, 1994, and continue at present; PiB PET imaging was initiated June 9, 2005. We included 70 individuals in the BLSA-NI with sleep data from a BLSA visit and an [11C]PiBPET scan less than 5 years after that visit.

The BLSA participants provided informed consent on enrollment and at subsequent visits. Study protocols were approved by institutional review boards affiliated with the National Institute on Aging Intramural Research Program and the Johns Hopkins Medical Institutions.

[11C]PiB PET Acquisition

Before undergoing [11C]PiB PET studies, participants were fitted with a thermoplastic face mask to decrease head motion. Scans in a 3-dimensional mode (Advance; General Electric) immediately after a mean (SD) intravenous bolus injection of 540 (33) megabecquerels of [11C]PiB. The PET data were acquired using the following protocol for the duration of the frames: 4 × 0.25 minutes, 8 × 0.50 minutes, 9 × 1.00 minute, 2 × 3.00 minutes, and 10 × 5.00 minutes (total, 70 minutes for 33 frames).

Magnetic Resonance Imaging Acquisition

Depending on the scan year, participants underwent imaging with 1 of 2 sequences on 1 of 3 devices. Five participants underwent a spoiled gradient-recalled acquisition sequence on a 1.5-T device (Signa; General Electric) (repetition time [TR], 35 milliseconds; echo time [TE], 5 milliseconds; flip angle 45°; image matrix, 256 × 256; 124 sections; pixel size, 0.94 × 0.94 mm; section thickness, 1.5 mm). A magnetization prepared rapid acquisition with gradient echo sequence was used for the other 65 participants. Of these, 42 underwent scanning on a 1.5-T device (Intera; Philips) (TR, 6.8 milliseconds; TE, 3.3 milliseconds; flip angle, 8°; image matrix, 256 × 256; 124 sections; pixel size, 0.94 × 0.94 mm; section thickness, 1.5 mm) and the remaining 23 on a 3-T scanner (Achieva; Philips) (TR, 6.8 milliseconds; TE, 3.2 milliseconds; flip angle, 8°; image matrix, 256 × 256; 170 sections; pixel size, 1 × 1 mm; section thickness, 1.2 mm). Magnetic resonance imaging (MRI) was performed at the same study visit as the PiB PET scanning.

Image Processing

Dynamic [11C]PiB PET images (70 minutes) were processed using an in-house pipeline with the Java Image Science Toolkit10 that was developed for the Medical Image Processing Analysis and Visualization program.11 The pipeline involved a radiofrequency coil inhomogeneity correction12 and segmentation13,14 of the MRIs to define the cerebellar gray matter reference region that was subsequently registered to the time-aligned PET; a multiple-atlas approach using 4 templates5 with cortical region delineations to define regions of interest using nonlinear deformation46 for label registration with subsequent label fusion77 on each individual’s MRI; model fitting of the PET image to generate voxel-based distribution volume ratios (DVRs) and parametric images18; and transformation of the MRI-based segmentation and labels onto the PET images for calculation of regional DVR and mean cortical DVR (cDVR).

We studied the following 2 PiB indices: mean cDVR and precuneus DVR. Mean cDVR is the weighted mean of values for the superior, middle, and inferior frontal regions; orbitofrontal, superior parietal, supramarginal, and angular gyrus; precuneus; superior, middle, and inferior occipital regions; superior, middle, and inferior temporal regions; and anterior, middle, and posterior cingulate regions. Cortical DVR provides a global index of cortical Aβ burden. Precuneus DVR was examined separately because the precuneus is likely affected early in the course of AD.19

Sleep Assessment

Participants reported in a standardized interview the mean number of hours of sleep obtained each night during the prior month using the following response options: “more than 7”; “more than 6, up to 7”; “more than 5, up to 6”; or “5 or fewer.” Responses were coded 0 to 3; each 1-unit increase indicated at least a 1-hour decrease in sleep duration. Participants also completed a modified version of the 5-item Women’s Health Initiative Insomnia Rating Scale (WHIIRS).20 This version queried about sleep during the past month rather than the prior 4 weeks and was administered by interview rather than questionnaire. The first 4 WHIIRS items query about how often respondents “have trouble falling asleep,” “wake up several times at night,” “wake up earlier than you planned to,” and “have trouble getting back to sleep” after early waking.20 Participants indicated the frequency of these problems on a 5-point scale (0 to ≥5 times per week). On the fifth WHIIRS item, respondents rate their sleep quality on a 5-point scale (ranging from “very sound or restful” to “very restless”). Responses are summed, yielding a total score; higher scores on items or the total score indicate more frequent sleep disturbance or worse sleep quality.20
Other Measures
Participants provided demographic data on enrollment. At imaging study visits, participants completed a neuropsychological test battery, including the Clinical Dementia Rating Scale. Data were reviewed at a case conference for all autopsies and for nonautopsy participants with 4 or more errors on the Blessed Information Memory Concentration Test. Mild cognitive impairment (MCI) was diagnosed using Petersen criteria, and dementia diagnoses followed Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised) criteria. Depressive symptoms were assessed using the 20-item Center for Epidemiological Studies–Depression Scale. Data were reviewed at a case conference for all autopsies and for nonautopsy participants with 4 or more errors on the Blessed Information Memory Concentration Test. Mild cognitive impairment (MCI) was diagnosed using Petersen criteria, and dementia diagnoses followed Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised) criteria. Depressive symptoms were assessed using the 20-item Center for Epidemiological Studies–Depression Scale.

Statistical Analysis
First, we explored the distributions of and correlations among responses to WHIIRS items and the distribution of sleep duration data. Responses to 2 WHIIRS items (ie, early waking and difficulty falling asleep after early waking) were highly correlated with other items or had a limited distribution. Thus, we did not consider these items as individual predictors but included them in the WHIIRS total score calculation. Next, we fit unadjusted and multivariable-adjusted linear regression models with continuous cDVR or precuneus DVR as the outcome. The primary predictors included sleep duration, difficulty falling asleep, waking several times, sleep quality ratings, or the WHIIRS total score, with each predictor analyzed in a separate model. To account for cardiovascular or pulmonary disease, we created a dichotomous variable indicating a history of heart attack or myocardial infarction, heart failure or congestive heart failure, angina, coronary bypass surgery or angioplasty, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease. Multivariable-adjusted models included age, sex, race, Center for Epidemiological Studies–Depression Scale score, body mass index (calculated as weight in kilograms divided by height in meters squared), APOE e4 status, history of cardiovascular or pulmonary disease, and current use of sleep medication (any vs none) as covariates. Pearson correlations were calculated to quantify associations between sleep variables and continuous outcomes. We conducted 2 sets of sensitivity analyses. In the first, we reran analyses after excluding participants with a diagnosis of MCI or dementia. In the second, to assess how robust our results were to the assumption of the data distribution, we fit logistic regression models with dichotomous (ie, elevated vs low PiB retention levels) versions of the cDVR (≥1.13) and precuneus DVR (≥1.38). Cut points for these variables were selected based on the clustering of DVRs in our sample (Supplement eFigure). Predictors and covariates were obtained from the study visit closest to the PiB PET scans. Unless otherwise indicated, data are expressed as mean (SD).

Results
The mean age of the participants when they completed the PiB PET scan was 78.2 (7.9) years; when they completed sleep measures, 76.4 (8.0); range, 52-91) years (Table 1). Sleep assessment occurred concurrently with or before the PiB PET scan. A mean lapse of 1.7 (1.6); range, 0.0-4.9) years occurred between PiB scanning and the most proximal sleep measure. Thirty-three participants (47%) were women, and 13 (19%) were black. Participants had a mean educational level of 16.8 (2.3); range, 12-20) years. At sleep assessment, their mean Mini-Mental State Examination score was 28.9 (1.6), and mean Center for Epidemiological Studies–Depression Scale score was 5.2 (5.7). Three participants had MCI and 1 had dementia. Two met MCI criteria at the time of sleep assessment; 3 met MCI criteria and 1 met dementia criteria at the PiB assessment. Seven participants (10%) used sleep medication during the prior month.

All 70 participants had PiB PET and sleep data from BLSA interviews occurring from 2004 or later; 62 participants had data on sleep duration. Overall, 24 participants (34%) had elevated PiB levels according to cDVR and 16 (23%) had elevated PiB levels according to the precuneus DVR. Twenty-six participants with sleep duration data (42%) reported more than 6 to no more than 7 hours of sleep per night; 19 (31%), more than 7 hours. However, 13 participants (21%) reported more than 5 to no more than 6 hours and 4 (7%), no more than 5 hours (Table 2). Their mean WHIIRS total score was 7.1 (4.3); range, 0-19); the distribution of responses to individual items is presented in Table 2.
In adjusted analyses, each 1-unit decrease in sleep duration was associated with a 0.08-point increase in cDVR (B = 0.08 [95% CI, 0.03-0.14]; partial r = 0.38; P = .005) (Table 3). This association is evident when unadjusted mean cDVR images are compared as a function of sleep duration (Figure). We found a comparable association between shorter sleep duration and precuneus DVR. In addition, each 1-unit increase in sleep-quality rating (i.e., worsening sleep quality) was associated with a 0.06-point increase in cDVR in unadjusted analysis (B = 0.06 [95% CI, 0.01-0.10]; P = .02); this result became nonsignificant after adjustment (Table 3). However, worse sleep quality was associated with a greater precuneus DVR in unadjusted and adjusted analyses (adjusted B = 0.08 [95% CI, 0.01-0.15]; partial r = 0.29; P = .03). We found no association between waking severe times and the cDVR or the precuneus DVR, but we found a trend toward an association between greater frequency of difficulty falling asleep and the cDVR and precuneus DVR in unadjusted and adjusted analyses and between the WHIIRS total score and the cDVR and precuneus DVR in unadjusted analyses.

After removing the 4 participants with MCI or dementia, associations remained in adjusted models between shorter sleep duration and cDVR (B = 0.07 [95% CI, 0.01-0.14]; partial r = 0.32; P = .02) and precuneus DVR (B = 0.10 [0.02-0.18]; partial r = 0.32; P = .02). The association between worse sleep quality and Aβ burden remained for the precuneus DVR in the unadjusted analyses (B = 0.08 [95% CI, 0.01-0.14]; r = 0.27; P = .02) and after adjustment (0.08 [0.01-0.15]; partial r = 0.29; P = .03).

In our sensitivity analysis examining the association between sleep variables and elevated PiB levels, results indicated that reports of shorter sleep duration and more frequent difficulty falling asleep each were associated with an
increased odds of elevated PiB levels according to the cDVR and precuneus DVR; poorer sleep quality was associated with a greater odds of elevated PiB levels as measured by the precuneus DVR (Supplement [eTable]). These associations remained after removing the 4 participants with MCI or dementia (data not shown).

Discussion
We examined the association between self-report indices of sleep and Aβ deposition measured by [11C]PiB PET in community-dwelling older adults. After adjustment for potential confounders, shorter sleep duration was associated with greater Aβ burden on continuous measures of cDVR and precuneus DVR, and worse sleep quality was associated with greater Aβ burden according to continuous precuneus DVR. Further, these associations remained after excluding participants with MCI or dementia, and we observed a similar pattern of associations when using a dichotomous outcome (elevated vs low PiB levels). Participant-reported frequency of multiple awakenings and a global index of disturbed sleep were not associated with Aβ burden. To our knowledge, this study is the first published to document associations between self-reported sleep and [11C]PiB PET-measured Aβ deposition in community-dwelling older adults.

Figure. Unadjusted Distribution Volume Ratios (DVRs) of Carbon 11–Labeled Pittsburgh Compound B Positron Emission Tomography Images by Sleep Duration

Images from 4 axial sections demonstrate that shorter self-reported sleep duration is associated with greater β-amyloid (Aβ) burden. Participants reporting more than 7 hours of sleep (n = 19) have the least Aβ burden, those reporting no more than 6 hours (n = 17) have the most, and those reporting more than 6 to no more than 7 hours (n = 26) have an intermediate level of burden. The rightmost column contains structural images from the Montreal Neurological Institute (MNI) space template.28,29 Scale represents DVR.
Our results are consistent with those from animal research in which sleep deprivation increased interstitial fluid Aβ levels.7 These studies raise the possibility that poor sleep may promote Aβ deposition, but they also raise questions about the mechanisms linking sleep/wake patterns and Aβ burden. Wake-related increases in neuronal activity have been suggested to mediate the association between sleep and Aβ levels.7 Indeed, in AD animal models and cultured hippocampal sections, increased neuronal activity promotes generation of Aβ peptide30-32; the sleep state is correlated with decreases and the wake state with increases in synaptic strength.23,34 Recent functional neuroimaging findings also suggest that excessive neuronal excitability may contribute to AD pathogenesis.35

Our results may have significant public health implications. Alzheimer disease is the most common form of dementing illness, and almost half of older adults report insomnia symptoms.36 Because late-life sleep disturbance can be treated, interventions to improve sleep or maintain healthy sleep among older adults may help prevent or slow AD to the extent that poor sleep promotes AD onset and progression. This result would have a substantial effect on the independence and quality of life of older adults and their families and on the significant health care costs associated with AD.

The present study has several strengths, including a well-characterized community-dwelling sample, assessment of multiple sleep variables, and use of [11C]PiB PET imaging. However, the study also has limitations. First, because our design is cross-sectional, we cannot tell whether sleep disturbance precedes Aβ deposition, limiting our ability to evaluate the direction of a potential causal association between poor sleep and AD. Indeed, a recent study in an AD mouse model37 showed that Aβ aggregation is accompanied by increased sleep/wake disruption and alterations in diurnal fluctuation of Aβ levels in interstitial fluid and that immunization with Aβ42 peptide decreases Aβ aggregation and preserves sleep/wake patterns and diurnal interstitial fluid fluctuation. Another recent study that measured sleep using actigraphy38 demonstrated that, compared with individuals without preclinical AD, those with preclinical AD (measured by cerebrospinal fluid levels of Aβ42) spend a smaller proportion of time in bed asleep (ie, they have lower sleep efficiency). A previous study39 has suggested that, although poor sleep may promote initial Aβ aggregation, Aβ deposition may promote derangements of sleep/wake patterns that feed forward to promote Aβ deposition and that prospective studies are needed to characterize the association between sleep/wake disruption and Aβ deposition. A second limitation of our study is that our sleep measures were based on self-report and did not include objective measures (eg, wrist actigraphy, polysomnography). Self-report sleep measures can be influenced by lower cognitive function39 and in some cases are only modestly correlated or even uncorrelated with objective sleep measures.40 Replication of findings using objective sleep measures would clarify whether perceptions of poor sleep and objective sleep indices are differentially associated with the pathological features of AD. Third, the prevalence of sleep-related breathing disorder increases with age41 and has been linked to MCI and dementia.42 Studies using polysomnography are needed to investigate whether sleep-related breathing disorder contributes to Aβ deposition43 and whether sleep-related breathing disorder drives the association we observed between poor sleep quality and Aβ burden. Finally, in our sleep-duration measure, the response option for those with the longest sleep duration was more than 7 hours, placing those obtaining 8 hours of sleep in the same category as those obtaining 11 hours. Consequently, we could not test hypotheses about very long sleep duration compared with more intermediate sleep duration (eg, 7-8 hours), with respect to Aβ burden.

In summary, our findings in a sample of community-dwelling older adults indicate that reports of shorter sleep duration and poorer sleep quality are associated with a greater Aβ burden. As evidence of this association accumulates, intervention trials will be needed to determine whether optimizing sleep can prevent or slow AD progression.

**ARTICLE INFORMATION**

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Self-reported Sleep and β-Amyloid Deposition

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