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Self-Reported Sleep and β-Amyloid Deposition in Community-Dwelling Older Adults

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Abstract

Importance—Older adults commonly report disturbed sleep, and recent studies in humans and animals suggest links between sleep and Alzheimer disease biomarkers. Studies are needed that evaluate whether sleep variables are associated with neuroimaging evidence of β-amyloid deposition.

Objective—To determine the association between self-reported sleep parameters and β-amyloid deposition in community-dwelling older adults.

Design—cross-sectional

Setting—Baltimore Longitudinal Study of Aging, a prospective study of normative aging

Participants—70 adults (mean age = 76; range 53 - 91) in the BLSA neuroimaging study

Main Outcome Measure—β-amyloid burden, measured by [^{11}C] Pittsburgh compound B (PiB) positron emission tomography (PET) distribution volume ratios (DVR)

Results—After adjustment for potential confounders, reports of shorter sleep duration were associated with greater β-amyloid burden, measured by mean cortical DVR (cDVR; B = 0.08, 95% confidence interval (CI) 0.03, 0.14, $p = 0.005$) and precuneus DVR (B = 0.11, 95% CI 0.03, 0.18, $p = 0.007$). Reports of lower sleep quality were associated with greater β-amyloid burden measured by precuneus DVR (B = 0.08, 95% CI 0.01, 0.15, $p = 0.025$).

Conclusions—Among community-dwelling older adults, reports of shorter sleep duration and lower sleep quality are associated with greater β-amyloid burden. Further studies with objective sleep measures are needed to determine whether sleep disturbance causes or accelerates Alzheimer disease.

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Introduction

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, 2] and have more fragmented sleep than those without AD,[1-3] 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, measured using wrist actigraphy, is associated with lower cognitive performance in community-dwelling elders.[6] While these findings indicate that sleep disturbance is associated with poor cognitive outcomes, it remains unclear whether poor sleep contributes to the neuropathology underlying cognitive decline.

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

We used data from community-dwelling participants in the Baltimore Longitudinal Study of Aging (BLSA) to investigate whether self-reported sleep parameters were associated with fibrillar β-amyloid burden, measured *in vivo* with [^{11}C] Pittsburgh compound B (PiB) positron emission tomography (PET). We hypothesized that reports of more fragmented sleep, shorter sleep duration, and lower sleep quality would be associated with greater amyloid burden.

Methods

Participants

We studied participants in the BLSA neuroimaging study (BLSA-NI),[8] a substudy of the larger BLSA study of normative aging.[9] Upon enrollment, BLSA participants must be free of cognitive impairment, mobility limitations and physical disability, major diseases (other than controlled hypertension) and conditions that can negatively affect functioning or life expectancy, or require ongoing antibiotic, immunosuppressant, corticosteroid, chronic pain medication or H2 blockers. At study visits, participants spend >48 consecutive hours at the BLSA Clinical Laboratory, where they have their height and weight measured, undergo a medical exam, complete multiple questionnaires and measures of cognition and physical function, and provide blood and urine for assays.

BLSA participants were eligible for the BLSA-NI (1994-present) if they were free of neurological disease, significant cardiovascular and pulmonary disease, and metastatic cancer at the BLSA-NI baseline. We studied 70 individuals in the BLSA-NI with sleep data from a BLSA visit and a [^{11}C]PiB PET scan <5 years after that visit.

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

[^{11}C]PiB PET Acquisition

Prior to [^{11}C]PiB PET studies, participants were fitted with a thermoplastic face mask to decrease head motion. Scans were conducted on a GE Advance scanner in 3-dimensional

mode immediately following an intravenous bolus injection of 14.6 ±0.90 mCi of [^{11}C]PiB. PET data were acquired per the following protocol for the duration of the frames: 4×0.25, 8×0.5, 9×1, 2×3, and 10×5 min (70 min total, 33 frames).

MRI Acquisition

Depending on scan year, participants were imaged with a spoiled gradient-recalled (SPGR) acquisition sequence (N=5; GE Signa 1.5T, TR=35ms, TE=5ms, α=45°, 256×256 image matrix, 124 slices, pixel size=0.94×0.94 mm, slice thickness=1.5 mm) or a magnetization prepared rapid acquisition with gradient echo (MPRAGE) sequence (N=65 total; for N=42 subjects a Philips 1.5T scanner was used with TR=6.8ms, TE=3.3ms, α=8°, 256×256 matrix, 124 slices, pixel size=0.94×0.94 mm, slice thickness=1.5 mm; and for the remaining N=23 subjects a Philips Intera 3T scanner was used with TR=6.8ms, TE=3.2ms, α=8°, 256×256 matrix, 170 slices, pixel size = 1×1 mm, slice thickness=1.2 mm). MR images were obtained at the same study visit as PiB images.

Image Processing

Dynamic [^{11}C]PiB PET images (70 minutes) were processed using an in-house pipeline with the Java Image Science Toolkit (JIST)[10] that was developed for the Medical Image Processing, Analysis and Visualization program (MIPAV).[11] The pipeline involved: RF coil inhomogeneity correction[12] and segmentation[13, 14] of the MRI to define the cerebellar gray matter reference region which was subsequently registered to the time-aligned PET; a multi-atlas approach using four templates[15] with cortical region delineations to define regions of interest using non-linear deformation[16] for label registration with subsequent label fusion[17] on each individual's MRI; model fitting of the PET image to generate voxel-based DVR and R1 parametric images[18]; and transformation of the MRI-based segmentation and labels onto the PET images for calculation of regional and mean cortical DVR.

We studied two PiB indices: mean cortical DVR (cDVR) and precuneus DVR. cDVR is the weighted average of values for the superior, middle and inferior frontal and orbitofrontal, superior parietal, supramarginal and angular gyrus regions, precuneus, superior, middle and inferior occipital, superior, middle and inferior temporal, anterior, middle and posterior cingulate regions. cDVR provides a global index of cortical β-amyloid burden. Precuneus DVR was examined separately because it is likely a region affected early in the AD course.[19]

Sleep Assessment

Participants reported in a standardized interview the average number of hours of sleep obtained each night over 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 one-unit *increase* indicated at least a one-hour *decrease* in sleep duration. Participants also completed a modified version of the five-item Women's Health Initiative Insomnia Rating Scale (WHIIRS).[20] This version queried about sleep over the past month, rather than the prior four weeks, and was administered by interview, rather than questionnaire. The first four 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 five-point scale (0 to ≥5 times per week). On the fifth WHIIRS item, respondents rate their sleep quality on a five-point scale (“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 upon enrollment. At imaging study visits, participants completed a neuropsychological test battery, including Clinical Dementia Rating Scale (CDR) administration.[21] Data were reviewed at a case conference for all autopsy participants and to non-autopsy participants with ≥4 errors on the Blessed-Information-Memory-Concentration Test.[22] Mild cognitive impairment (MCI) was diagnosed using Petersen criteria[23] and dementia diagnoses followed Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) criteria.[24] Depressive symptomatology was assessed with the 20-item Center for Epidemiological Studies-Depression Scale (CES-D).[25] At each BLSA visit, a nurse practitioner conducts an interview covering signs, symptoms, and diagnosed health conditions, and reviews medical records to obtain a medical history. Participants also reported frequency of sleep medication use over the prior month on a five-point scale (0 to ≥5 times per week). Apolipoprotein E (APOE) genotype (e4 carrier vs. non-carrier) was measured in BLSA participants because the e4 allele is a potent risk factor for AD[26] and APOE is associated with brain amyloid burden.[27]

Statistical Analysis

First, we explored distributions of, and correlations among responses to WHIIRS items, and the distribution of sleep duration data. Responses to two WHIIRS items (i.e., early waking, 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 they were included in the WHIIRS total score calculation. Next, we fit unadjusted and multivariable (MV)-adjusted linear regression models with either 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, with each predictor analyzed in a separate model. To account for cardiovascular or pulmonary disease, we created a dichotomous variable indicating history of heart attack or myocardial infarction, heart failure or congestive heart failure, angina, coronary bypass surgery or angioplasty, chronic bronchitis, emphysema, or COPD. MV-adjusted models included age, sex, race, CES-D score, body mass index (BMI; kg/m^2), APOE e4 status, history of cardiovascular or pulmonary disease, and current sleep medication use (any vs. none) as covariates. Partial correlations were calculated to quantify associations between sleep variables and continuous outcomes, after controlling for covariates. We conducted two sets of sensitivity analyses. In the first, we re-ran analyses after excluding participants with an MCI or dementia diagnosis. In the second, to assess how robust our results were to the assumption of the data distribution, we fit logistic regression models with dichotomous (i.e., elevated vs. low PiB binding) versions of the cDVR (≥1.125) and precuneus DVR (≥1.38). Cutpoints for these variables were selected based on the clustering of DVRs in our sample (eFigure 1). Predictors and covariates were from the study visit closest to PiB PET scans.

Results

Participants were aged (mean ±standard deviation) 78.2 ±7.9 years when they completed PiB PET, and 76.4 ±8.0 (range 53 – 91) when they completed sleep measures; sleep assessment occurred concurrently with or prior to PiB PET. There were 1.7 ±1.6 years (range 0.0-4.9) between PiB and the most proximal sleep measure (Table 1). Thirty-three participants (47.1 %) were women, and 13 (18.6%) were Black. Participants had 16.8 ±2.3 years of education (range 12-20), and at sleep assessment, their mean MMSE score was 28.9 ±1.6, and mean CES-D score was 5.2 ±5.7. Three participants had MCI and 1 had dementia. Two met MCI criteria at the time of sleep assessment, and three met MCI criteria and one

met dementia criteria at PiB assessment. Seven (10.0%) took sleep medication over the prior month.

Seventy participants had both PiB PET data and sleep data from BLSA interviews occurring at or after 2004; 62 participants had data on sleep duration. Overall, 24 participants (34.3%) had elevated PiB according to cDVR and 16 (22.9%) had elevated PiB in precuneus. Forty-two percent reported >6 to ≤7 hours of sleep per night and 31% reported >7 hours; however, 21% reported >5 to ≤6 hours and 7% reported ≤5 hrs (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 one-unit decrease in sleep duration was associated with a 0.08-point increase in cDVR (B = 0.08, 95% confidence interval (CI) 0.03, 0.14, partial $r = 0.38$, $p = 0.005$) (Table 3). This association is evident when unadjusted mean cDVR images are compared as a function of sleep duration (Figure 1). There was a comparable association between shorter sleep duration and precuneus DVR. In addition, each one-unit increase in sleep quality rating (i.e., worse sleep quality) was associated with a 0.06-point increase in cDVR in unadjusted analyses (B = 0.06, 95% CI 0.01, 0.10, $p = 0.019$); this became non-significant after adjustment. Worse sleep quality was associated with greater precuneus DVR, however, in unadjusted and adjusted analyses (adjusted B = 0.08, 95% CI 0.01, 0.15; partial $r = 0.29$, $p = 0.025$). There was no association between waking several times and either cDVR or precuneus DVR, but there was a trend toward an association between greater frequency of difficulty falling asleep and both cDVR and precuneus DVR in unadjusted and adjusted analyses, and between WHIIRS total scores and both cDVR and precuneus DVR in unadjusted analyses.

After removing the four participants with MCI or dementia, associations remained in adjusted models between shorter sleep duration and both cDVR (B = 0.07, 95% CI 0.01, 0.14, partial $r = 0.32$, $p = 0.019$) and precuneus DVR (B = 0.10, 95% CI 0.02, 0.18, partial $r = 0.32$, $p = 0.021$). The association between worse sleep quality and amyloid burden remained for precuneus DVR in both unadjusted analyses (B = 0.08, 95% CI 0.01, 0.14, partial $r = 0.27$, $p = 0.020$), and after adjustment (B = 0.08, 95% CI 0.01, 0.15, partial $r = 0.29$, $p = 0.028$).

In our sensitivity analysis examining the association between sleep variables and elevated PiB, results indicated that reports of shorter sleep duration and more frequent difficulty falling asleep each were associated with an increased odds of elevated PiB according to both cDVR and precuneus DVR; lower sleep quality was associated with a greater odds of elevated PiB as measured by precuneus DVR (eTable 1). These associations remained after removing the four participants with MCI or dementia (data not shown).

Comment

We examined the association between self-report indices of sleep and β-amyloid deposition, measured by [^{11}C]PiB PET, in community-dwelling older adults. After adjustment for potential confounders, shorter sleep duration was associated with greater amyloid burden on continuous measures of cortical DVR (cDVR) and precuneus DVR, and worse sleep quality was associated with greater β-amyloid burden according to continuous precuneus DVR. Further, these associations remained after excluding participants with either MCI or dementia, and we observed a similar pattern of associations when using a dichotomous outcome (elevated vs. low PiB). Neither participant-reported frequency of multiple awakenings nor a global index of disturbed sleep was associated with β-amyloid burden. To

our knowledge, this is the first published study of self-reported sleep and PiB PET-measured β-amyloid deposition in community-dwelling older adults.

Our results are consistent with those from animal research in which sleep deprivation increased ISF β-amyloid.[7] These studies raise the possibility that poor sleep may promote amyloid deposition, but they also raise questions about mechanisms linking sleep/wake and amyloid burden. It has been suggested that wake-related increases in neuronal activity may mediate the association between sleep and β-amyloid levels.[7] Indeed, in AD animal models and cultured hippocampal slices, increased neuronal activity promotes generation of Aβ peptide,[28-30] and the sleep state is correlated with decreases, and the wake state with increases in synaptic strength.[31, 32] Recent functional neuroimaging findings also suggest that excess neuronal excitability may contribute to AD pathogenesis.[33]

Our results may have significant public health implications. AD is the most common form of dementing illness, and almost half of older adults report insomnia symptoms.[34] Because late-life sleep disturbance can be treated, to the extent that poor sleep promotes AD onset and progression, interventions to improve sleep or maintain healthy sleep among older adults may help prevent or slow AD. This would have a substantial impact on independence and quality of life of older adults and their families, and on the significant healthcare costs associated with AD.

The present study has several strengths, including a well-characterized community-dwelling sample, assessment of multiple sleep variables, and [^{11}C]PiB PET imaging. However, it also has limitations. First, because it is cross-sectional in design, we cannot tell whether sleep disturbance preceded β-amyloid 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 model showed that Aβ aggregation is accompanied by increased sleep/wake disruption and alterations in diurnal fluctuation of Aβ in ISF, and that immunization with $A\beta_{1\text{-}42}$ decreases Aβ aggregation and preserves sleep/wake patterns and diurnal ISF fluctuation.[35] Another recent study that measured sleep using actigraphy demonstrated that, compared to those without preclinical AD, humans with preclinical AD (measured by CSF Aβ42) spend a smaller proportion of time in bed asleep (i.e., they have lower sleep efficiency).[36] It has been suggested that, while poor sleep may promote initial Aβ aggregation, amyloid deposition may promote derangements of sleep/wake that feed forward to promote amyloid deposition, and that prospective studies are needed to characterize the association between sleep/wake disruption and amyloid deposition.[35] A second limitation of our study is that our sleep measures were based on self-report and did not include objective measures (e.g., wrist actigraphy, polysomnography). Self-report sleep measures can be influenced by lower cognitive function,[37] and in some cases are only modestly correlated or even uncorrelated with objective sleep measures.[38] Replication of findings using objective sleep measures would clarify whether perceptions of poor sleep and objective sleep indices are differentially associated with AD pathology. Third, the prevalence of sleep-disordered breathing (SDB) increases with age,[39] and SDB has been linked to mild cognitive impairment and dementia.[40] Studies using polysomnography are needed to investigate whether SDB contributes to β-amyloid deposition,[41] and whether SDB drives the association we observed between poor sleep quality and β-amyloid burden. Finally, in our sleep duration measure, the response option for those with the longest sleep duration was “>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 sleepers compared to those with more intermediate sleep duration (e.g., 7 to 8 hours), with respect to β-amyloid burden.

Conclusions

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Susan Resnick had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Yang An, M.S. (Intramural Research Program, National Institute on Aging, National Institutes of Health) performed the statistical analysis, Murat Bilgel, B.S. (Intramural Research Program, National Institute on Aging, National Institutes of Health and Department of Biomedical Engineering, Johns Hopkins University) performed the image analysis, Adam P. Spira, Ph.D. (Department of Mental Health, Johns Hopkins Bloomberg School of Public Health), and Susan M. Resnick, Ph.D. (Intramural Research Program, National Institute on Aging, National Institutes of Health) supervised the statistical and image analysis and assume responsibility for the overall analysis.

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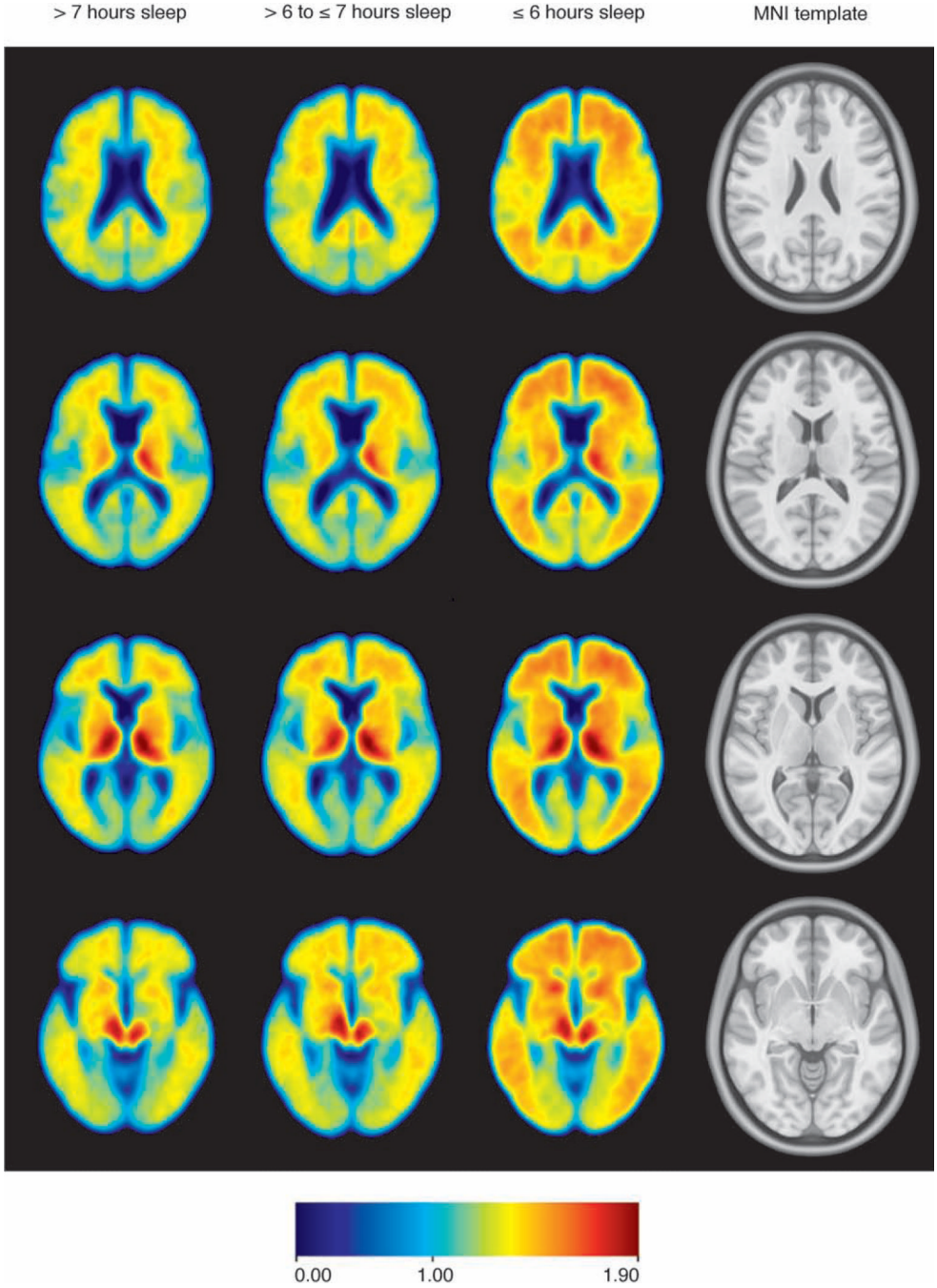

Figure 1.

Unadjusted mean PiB DVR images from four axial slices demonstrate that shorter self-reported sleep duration is associated with greater β-amyloid burden. Participants reporting >7 hours sleep (n = 19) have the least amyloid burden, those reporting ≤6 hours sleep duration (n = 17) have the most, and those reporting >6 to ≤7 hours (n = 26) have an intermediate level of burden. Rightmost column contains structural images from the Montreal Neurological Institute space template.[42, 43]

Table 1

Participant characteristics.

	Mean ±SD or *n* (%)
Female sex	33 (47.1)
Black race	13 (18.6)
Education (years)	16.8 ±2.3
Age at sleep assessment (years)	76.4 ±8.0
Age at PiB PET (years)	78.2 ±7.9
Interval between sleep and PiB PET (years)	1.7 ±1.6
CES-D (0 to 60)	5.2 ±5.7
PiB cDVR	1.12 ±0.19
PiB precuneus DVR	1.25 ±0.26
Elevated cDVR	24 (34.3)
Elevated precuneus DVR	16 (22.9)
Body mass index (kg/m^2)	27.2 ±4.1
APOE e4-positive	20 (28.6)
MMSE (0 to 30)	28.9 ±1.6
CVD or pulmonary disease	9 (12.9)
Takes any sleep medication	7 (10.0)

Note: N = 70. APOE = apolipoprotein E; CES-D = Center for Epidemiological Studies Depression Scale; CVD = cardiovascular disease; MMSE = Mini-Mental State Examination.

Table 2

Distribution of sleep characteristics over the past month.

Average hours of sleep	***n* (%)**
>7	19 (30.6)
>6 to ≤7	26 (41.9)
>5 to ≤6	13 (21.0)
≤5	4 (6.5)

Trouble falling asleep[a]	***n* (%)**
none	39 (55.7)
<1 time/week	9 (12.9)
1−2 times/week	15 (21.4)
3−4 times/week	4 (5.7)
5+ times/week	3 (4.3)

Wake several times[a]	***n* (%)**
none	10 (14.3)
<1 time/week	10 (14.3)
1−2 times/week	6 (8.6)
3−4 times/week	5 (7.1)
5+ times/week	39 (55.7)

Sleep quality[a]	***n* (%)**
Very sound/restful	15 (21.4)
Sound/restful	20 (28.6)
Average quality	28 (40.0)
Restless	7 (10.0)
Very restless	0

N = 70 for all variables except average hours of sleep (*n* = 62).

[a]From the Women's Health Initiative Insomnia Rating Scale (WHIIRS).

Table 3

Association between sleep variables and continuous DVRs.

	Unadjusted			MV-adjusted		
	B (95% CI)	**Partial *r***	***p-value*** [a]	**B (95% CI)**	**Partial *r***	***p-value*** [a]
Shorter sleep duration						
cDVR	**0.06 (0.004, 0.11)**	**0.27**	**0.035**	**0.08 (0.03, 0.14)**	**0.38**	**0.005**
Precuneus DVR	**0.07 (0.0001, 0.14)**	**0.25**	**0.0498**	**0.11 (0.03, 0.18)**	**0.36**	**0.007**
Trouble falling asleep[b]						
cDVR	0.04 (−0.002, 0.07)	0.22	0.065	0.03 (−0.003, 0.07)	0.23	0.071
Precuneus DVR	0.04 (−0.007, 0.10)	0.20	0.091	0.05 (−0.005, 0.10)	0.23	0.076
Wake several times[b]						
cDVR	0.01 (−0.02, 0.04)	0.08	0.487	0.01 (−0.02, 0.04)	0.05	0.715
Precuneus DVR	0.01 (-0.03, 0.05)	0.07	0.561	0.01 (-0.03, 0.05)	0.05	0.690
Worse sleep quality[b]						
cDVR	**0.06 (0.01, 0.10)**	**0.28**	**0.019**	0.04 (−0.01, 0.09)	0.19	0.130
Precuneus DVR	**0.09 (0.03, 0.16)**	**0.34**	**0.004**	**0.08 (0.01, 0.15)**	**0.29**	**0.025**
WHIIRS total						
cDVR	0.01 (−0.0001, 0.02)	0.23	0.052	0.01 (−0.004, 0.02)	0.16	0.227
Precuneus DVR	0.01 (−0.0002, 0.03)	0.23	0.054	0.01 (−0.004, 0.02)	0.18	0.161

Note: *N* = 70 for all analyses except sleep duration *(N* = 62). MV-adjusted for age, sex, race, CES-D score, body mass index, APOE e4 status, cardiovascular or pulmonary disease, and use of sleep medication (any vs. none). Partial *r*'s are correlations between sleep variables and imaging outcomes after controlling for the same covariates included in MV analyses.

[a] *p*-values apply to regression coefficients and partial correlations.

[b] From the Women's Health Initiative Insomnia Rating Scale (WHIIRS; higher scores indicate worse sleep). B = unstandardized regression coefficient; cDVR = cortical distribution volume ratio; CI = confidence interval; MV = multivariable.