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RESEARCH ARTICLE

Association of Sleep Duration and Change Over Time With Imaging Biomarkers of Cerebrovascular, Amyloid, Tau, and Neurodegenerative Pathology

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Abstract

Background and Objectives

Both short and long sleep duration were previously associated with incident dementia, but underlying mechanisms remain unclear. We evaluated how self-reported sleep duration and its change over time associate with (A)myloid, (T)au, (N)eurodegeneration, and (V)ascular neuroimaging markers of Alzheimer disease.

Methods

Two Framingham Heart Study overlapping samples were studied: participants who underwent ^{11}C-Pittsburg Compound B amyloid and ^{18}F-flortaucipir tau PET imaging and participants who underwent an MRI. MRI metrics estimated neurodegeneration (total brain volume) and cerebrovascular injuries (white matter hyperintensities [WMHs] volume, covert brain infarcts, free-water [FW] fraction). Self-reported sleep duration was assessed and split into categories both at the time of neuroimaging testing and approximately 13 years before: short ≤6 hours. average 7–8 hours, and long ≥9 hours. Logistic and linear regression models were used to examine sleep duration and neuroimaging metrics.

Results

The tested cohort was composed of 271 participants (age 53.6 ± 8.0 years; 51% male) in the PET imaging sample and 2,165 participants (age 61.3 ± 11.1 years; 45% male) in the MRI sample. No fully adjusted association was observed between cross-sectional sleep duration and neuroimaging metrics. In fully adjusted models compared with consistently sleeping 7–8 hours, groups transitioning to a longer sleep duration category over time had higher FW fraction (short to average β [SE] 0.0062 [0.0024], $p = 0.009$; short to long β [SE] 0.0164 [0.0076], $p = 0.031$; average to long β [SE] 0.0083 [0.0022], $p = 0.002$), and those specifically going from average to long sleep duration also had higher WMH burden (β [SE] 0.29 [0.11], $p = 0.007$). The opposite associations (lower WMH and FW) were observed in participants consistently sleeping ≥9 hours as compared with people consistently sleeping 7–8 hours in fully adjusted models (β [SE] −0.43 [0.20], $p = 0.028$; β [SE] −0.019 [0.004], $p = 0.020$). Each hour of increasing sleep (continuous, β [SE] 0.12 [0.04], $p = 0.003$; β [SE] 0.002 [0.001], $p = 0.021$) and extensive increase in sleep duration (≥2 hours vs 0 ± 1 hour change; β [SE] 0.24 [0.10], $p = 0.019$; β [SE] 0.0081 [0.0025], $p = 0.001$) over time was associated with higher WMH burden and FW fraction in fully adjusted models. Sleep duration change was not associated with PET amyloid or tau outcomes.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ATV(N)** = amyloid tau vascular neurodegeneration; **FHS** = Framingham Heart Study; **FLAIR** = fluid-attenuated inversion recovery; **FLR** = frontal, lateral, and retrosplenial cortices; **FTP** = ^{18}F-flortaucipir; **FW** = free-water; **MCI** = mild cognitive impairment; **OR** = odds ratio; **PiB** = ^{11}C-Pittsburg Compound B; **ROI** = region of interest; **SUVr** = standardized uptake value ratio; **WMH** = white matter hyperintensity.

Discussion

Longer self-reported sleep duration over time was associated with neuroimaging biomarkers of cerebrovascular pathology as evidenced by higher WMH burden and FW fraction. A longer sleep duration extending over time may be an early change in the neurodegenerative trajectory.

Introduction

It has now been shown repeatedly that both self-reported short and long sleep duration are associated with increased Alzheimer disease (AD) dementia risk.[1] There is building evidence suggesting that dynamic changes in sleep quantity over the lifespan, namely lengthening or shortening of sleep duration over time, might also be associated with clinical AD risk. In our cohort, participants of the Framingham Heart Study (FHS) who reported long sleep duration, or changes toward longer sleep duration, had higher risk of incident dementia, including clinical AD.[2] The authors of a study[3] found that a 1-hour sleep duration increase over 12 years was associated with a 30% higher risk of incident dementia, whereas a 2-hour increase was associated with a 2-fold elevated risk of incident dementia. While both shortening and lengthening of sleep duration over time are associated with higher risk of developing mild cognitive impairment (MCI), higher odds ratios (ORs) were observed for sleep durations increasing by 2 hours or more over time.[4] Sleep duration and its change over time is thus associated with dementia risk, but the mechanisms are unclear. Specifically, it is not clear whether sleep duration associates with AD biology, including neuroimaging biomarkers. This is especially important in the context that sleep disturbances and sleep duration habits are modifiable through behavioral therapies.

The AT(N) framework proposed in 2018[5] highlights the importance of amyloid (A), tau (T), and neurodegeneration (N) biomarkers to study AD pathology. The β-amyloid (Aβ) and tau components can be measured through CSF or PET, whereas the neurodegenerative component is mostly assessed through neuroimaging measurements on MRI, such as atrophy. AT(N) might evolve to ATV(N) to include cerebrovascular biomarkers,[5] which are a key component of the pathologic cascade of AD. In fact, participants on the AD continuum according to AT(N) biomarkers or patients with AD often show many vascular changes and risk factors such as coronary heart disease, carotid artery stenosis, infarcts, cerebral amyloid angiopathy, atherosclerosis, and cortical microbleeds.[6,7] Although neuroimaging markers of actual cerebrovascular lesions are of interest (e.g., infarcts, lacunes), there are biomarkers that suggests vascular dysregulation earlier in the disease process, such as white matter hyperintensities (WMHs) or free-water (FW) imaging.[7]

The objective of this study was to evaluate how self-reported sleep duration and its change over time associates with ATV(N) neuroimaging markers of AD and cerebrovascular injury, to elucidate underlying mechanisms explaining the association between short and long sleep duration and incident AD.

Methods

Overview of the Sample

Within the FHS, a multigenerational community-based cohort, participants are evaluated with clinical examinations approximately every 4 years. Two samples were selected from the FHS cohorts.[8,9] The first was the MRI sample (n = 2,165), which included participants from both the Offspring and Third Generation cohorts at their ninth (2011–2014) and third (2016–2019) clinic examination, respectively. In this MRI sample, 170 people were excluded for prevalent dementia, stroke, or other neurologic diseases. The second sample with participants who underwent PET imaging (n = 271) was a subsample of the MRI sample and included participants from the FHS Third Generation cohort at their third clinic examination (2016–2019). Individuals selected for PET testing were free of dementia, stroke, or other neurologic diseases.

Standard Protocol Approvals, Registrations, and Patient Consents

Before the beginning of the study, all participants gave their written informed consent. The Boston University Medical Center review board approved the study.

Sleep Assessments

Cross-sectional Analyses

Participants were asked about their habitual self-reported sleep duration at their clinical examination, near the time of

the neuroimaging testing (referred to as follow-up, see "*Longitudinal analyses*" below). The question was phrased "Numbers of hours that you typically sleep." Categories were as follows: short sleep duration ≤6 hours, average sleep duration 7–8 hours, and long sleep duration ≥9 hours.

Longitudinal Analyses

The change in sleep duration was calculated between the first and third examination for the Third Generation (2002–2005 to 2016–2019) and between the seventh and ninth examination for the Offspring cohort (1998–2001 to 2011–2014). The question was identical at all time points and examinations. Therefore, the assessed changes in sleep duration occurred over 13 years on average before neuroimaging. The first clinic examination with sleep assessment is therefore referred to as "baseline," whereas the second clinic examination with sleep assessment that coincides with neuroimaging is referred to as "follow-up."

Amyloid and Tau Components: PET Acquisition and Processing

Aβ and tau were assessed with ^{11}C-Pittsburg Compound B (PiB) and ^{18}F-flortaucipir (FTP) PET imaging, respectively, on either a Siemens ECAT HR+ or GE Discovery MI PET/CT scanner, as previously described.[10-12] PiB-PET images were obtained with a 1-hour dynamic acquisition (10–15 mCi bolus injection). FTP-PET images were obtained with four 5-minute frames (9–11 mCi bolus injection). PET images were coregistered to T1 MRI images with FreeSurfer 6.0 and Statistical Parametric Mapping. Given the young age of the sample, we did not use partial volume correction. Left and right hemispheres were averaged for each region of interests (ROIs). PiB retention in each ROI estimating Aβ deposition was expressed as the distribution volume ratio with reference to the cerebellar cortex.[13] The frontal, lateral, and retrosplenial cortices (FLR) were combined together as a global PiB measure. The specific ROIs included in this FLR measurement (log-transformed for normality) were superior frontal gyrus, inferior frontal gyrus, rostral middle frontal gyrus, rostral anterior cingulate gyrus, medial orbitofrontal gyrus, inferior and middle temporal gyri, inferior parietal gyrus, and precuneus.[13]

FTP uptake estimating Tau was expressed as the standardized uptake value ratio (SUVr) with reference to the cerebellar cortex. The SUVr was computed in the following ROIs given the roles of these regions in AD progression and/or sleep regulation[11,12,14]: entorhinal and composite rhinal cortices, medial orbitofrontal gyrus, and rostral anterior cingulate cortex.

Neurodegeneration and Cerebrovascular Components: MRI Acquisition and Processing

Total brain volume was used as a neuroimaging marker of nonspecific neurodegeneration, whereas WMH, covert brain infarcts, and FW imaging were used as cerebrovascular markers.

MRI sequences (T1-weighted, fluid-attenuated inversion recovery [FLAIR], diffusion-weighted imaging) were acquired on 1.5 T Siemens Avanto scanner, as described previously.[15] MRI images were processed using atlas-based methods[16] according to published automated procedures.[15,17,18] Volumes of the total brain and WMH were extracted from FLAIR and T1-weighted images and expressed as a percentage of the total intracranial volume to remove head size effects. WMH volumes were log-transformed. The presence of extensive WMH for age was defined as a dichotomous variable: 1 SD above the age-adjusted mean of the cohort for the log of WMH volume/intracranial volume. The presence of covert brain infarcts were inspected visually to rate lesions ≥3 mm.[15] On the diffusion-weighted imaging sequence, FW was computed according to previously published algorithms.[19] FW corresponds to the fraction of unrestricted extracellular water in white matter, where a higher value is associated with ischemic vasogenic edema.[20]

Clinical Covariates

Genotyping the *APOE4* allele was made by PCR from whole blood (35 cycles, DNA Thermal Cycler, PTC-100; MJ Research). *APOE4* carriers were those with at least 1 *E4* allele. The presence of depressive symptoms was defined as a score on the Center for Epidemiologic Studies Depression Scale ≥16 and/or current antidepressant usage. The presence of hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. The presence of diabetes mellitus was defined as a fasting blood glucose level ≥126 mg/dL or use of oral hypoglycemic agents or insulin. The presence or history of a prevalent cardiovascular disease was defined as coronary heart disease, peripheral arterial disease, and/or heart failure.

Statistical Analysis

Statistical analyses were performed using SAS V9.4 (SAS Institute, Cary, NC). Missing variables were excluded analysis by analysis. All PET outcomes variables were standardized. p values <0.05 were considered statistically significant. Changes in self-reported sleep duration were treated continuously and categorically.

Cross-sectional Analyses

Linear regression models were used to evaluate the association between sleep duration categories (≤6 hours, 7–8 hours as reference, ≥9 hours) and PET and MRI outcomes representative of ATV(N) components. For dichotomous outcomes (WMH extensive for age, covert brain infarcts), logistic regression models were used. Model 1 included age, sex, and time between the clinic examination and neuroimaging. In analyses with PET outcomes, the PET camera was also entered as covariate because 2 cameras were used in this project. In analyses exploring MRI outcomes, age squared was also included as a covariate because the association between age and many MRI outcomes is nonlinear. Model 2 included model 1 covariates in addition to *APOE4* allele carrier status, depressive symptoms, diabetes, hypertension status, and prevalent cardiovascular diseases.

Longitudinal Analyses

Linear regression models were used to evaluate the association between changes in sleep duration categories over time, with stable average sleep duration over time used as reference (see categories below) and PET and MRI outcomes representative of ATV(N) components. For dichotomous outcomes (WMH extensive for age, covert brain infarcts), logistic regression models were used. Analyses with changes in sleep duration were only adjusted for model 1 covariates in the PET sample (age, sex, time between the clinic examination and neuroimaging testing, PET camera) because some sleep duration changes categories had a small number of participants reducing statistical power. In the larger MRI sample, models were adjusted for model 1 (age, sex, time between the clinic examination and neuroimaging testing, age squared) and model 2 covariates (model 1 covariates, *APOE4* allele carrier status, depression, diabetes, hypertension status, and prevalent cardiovascular diseases).

In the PET sample, the sample size did not allow some of the group comparisons, and thus, a few categories of sleep duration changes were combined. The following categories were compared with stable average sleep duration (7–8 hours) and combined as follows as:

1. Stable short sleep duration (≤6 hours). No participants had stable long sleep duration over time in the PET sample;
2. Transitioning to longer sleep duration, including average to long sleep duration (7–8 hours to ≥9 hours) and short to average/long sleep duration (≤6 hours to >6 hours);
3. Transitioning to shorter sleep duration, including long to average/short sleep duration (≥9 hours to <9 hours) and average to short sleep duration (7–8 hours to ≤6 hours).

Because the MRI sample was larger, all possible categories were compared with stable average sleep duration (7–8 hours):

1. Stable long sleep duration (≥9 hours);
2. Average to long sleep duration (7–8 hours to ≥9 hours);
3. Short to long sleep duration (≤6 hours to ≥9 hours);
4. Short to average sleep duration (≤6 hours to 7–8 hours);
5. Stable short sleep duration (≤6 hours);
6. Average to short sleep duration (7–8 hours to ≤6 hours);
7. Long to short sleep duration (≥9 hours to ≤6 hours);
8. Long to average sleep duration (≥9 hours to 7–8 hours).

We also investigated changes in sleep duration regardless of initial sleep categories 2 different ways in both the MRI and PET samples. Increases and decreases (separately) in sleep duration of ≥2 hours over time were compared for ATV(N) neuroimaging outcomes with those within an hour of change in either direction. In addition, because we expected a potential U-shape association, we explored continuous change in sleep duration with ATV(N) biomarkers in 2 separate subsamples: (1) those whose sleep duration did not change or increased over time and (2) those whose sleep duration did not change or decreased over time.

Data Availability

The FHS makes phenotypic and genetic data available through the online repositories BioLINCC and dbGaP, respectively.

Results

Sample Characteristics

Characteristics of the PET and MRI samples at both time points are presented in Table 1. The PET sample was younger than the MRI sample by approximately 8 years on average. Time between baseline and follow-up was 13.9 years on average in the PET sample and 13.1 years in the MRI sample. As compared with participants who underwent PET imaging for Aβ deposition, the PET imaging sample for tau uptake was slightly smaller. Approximately half of the participants had average sleep duration (7–8 hours) that remained stable over time. Moreover, 83%–85% of the sample had a sleep duration that remained relatively stable over time (±1 hour) independently of the sleep duration categories they fell in. Still, marked sleep duration changes occurred in both directions: 6%–8% of the sample showed increased sleep duration by ≥2 hours whereas 9% of the sample showed decreased sleep duration ≥2 hours over time.

eTables 1 and 2 (links.lww.com/WNL/D231) show characteristics of the samples split by sleep duration categories at follow-up (cross-sectionally), and eTable 3 shows average values of neuroimaging metrics in both samples. In brief, the long sleep duration category in both the MRI and PET samples tended to include slightly older participants with a higher proportion of participants with depression. In the PET sample alone, the longer sleep duration category included more men and participants with a higher body mass index.

Cross-sectional Analysis: Sleep Duration Categories and ATV(N) Neuroimaging Biomarkers

Associations between short and long sleep duration categories as compared with average sleep duration with ATV(N) neuroimaging biomarkers are shown in Table 2. No associations were observed between sleep duration categories and PET-derived Aβ and tau components nor with total brain volume as a marker of neurodegeneration. For cerebrovascular markers, average FW was higher in those with long sleep duration compared with average sleep duration when adjusting for model 1 covariates, but not when adjusting for model 2 covariates. When exploring

Table 1 Characteristics of the Cohort

Characteristics	PET sample		MRI sample	
	Baseline (2002–2005)	Follow-up (2016–2019)	Baseline (1998–2005)	Follow-up (2011–2019)
Total, N	271		2,165	
PET-tau subset, n (%)	237 (87)		—	
Sex, male participants, n (%)	138 (51)		982 (45)	
***APOE4* allele carriers, n (%)**	63 (23)		479 (23)	
Time between sleep assessments, y, mean ± SD	13.9 ± 0.6		13.1 ± 1.0	
Education, n (%)				
Unfinished high school	3 (1)		21 (1)	
High school degree	26 (10)		360 (17)	
Some college	74 (27)		608 (28)	
College graduate	167 (62)		1,176 (54)	
Age, y, mean ± SD	39.7 ± 8.0	53.6 ± 8.0	48.2 ± 11.6	61.3 ± 11.1
Systolic BP, mm Hg, mean ± SD	117 ± 15	120 ± 14	119 ± 15	122 ± 15
Antihypertension usage, n (%)	23 (8)	63 (24)	308 (14)	793 (37)
Body mass index, kg/m^2, mean ± SD	26.8 ± 5.1	28.8 ± 5.6	27.2 ± 5.1	28.4 ± 5.4
Cardiovascular disease, n (%)	2 (1)	8 (3)	68 (3)	162 (7)
Diabetes, n (%)	6 (2)	22 (8)	83 (4)	211 (10)
Depression, n (%)	46 (17)	65 (24)	354 (19)	502 (28)
Self-reported sleep duration, h, mean ± SD	7.2 ± 0.90	7.1 ± 1.0	7.2 ± 1.0	7.2 ± 1.2
Distribution of sleep duration changes over time from baseline to follow-up, n (%)				
Stable average sleep duration	153 (56)		1,114 (51)	
Stable long sleep duration	0		47 (2)	
Average to long sleep duration	12 (4)		167 (8)	
Short to long sleep duration	1 (0)		14 (1)	
Short to average sleep duration	22 (8)		213 (10)	
Stable short sleep duration	28 (10)		230 (11)	
Average to short sleep duration	46 (17)		281 (13)	
Long to short sleep duration	1 (0)		12 (1)	
Long to average sleep duration	8 (3)		87 (4)	
No change in sleep hours (0 ± 1 h)	230 (85)		1,806 (83)	
Increased by 2 h or more	17 (6)		174 (8)	
Decreased by 2 h or more	24 (9)		185 (9)	

Abbreviation: BP = blood pressure.
Short sleep duration ≤6 hours, average sleep duration 7–8 hours, and long sleep duration ≥9 hours.

which variables were confounding in model 2, depression affected the significance of findings between long sleep duration and FW (β [SE] 0.005 [0.002], p = 0.018 when depression is removed from model 2). When stratified by depression status, no associations were observed in nondepressed participants. In depressed participants, long sleep was associated with higher FW fraction when adjusting for model 1 (β [SE] 0.007 [0.004], p = 0.049) with similar effect size for short sleep (β [SE] 0.005

Table 2 ATV(N) Neuroimaging Biomarkers With Cross-sectional Short and Long Sleep Duration

Outcomes	Models	Sleep duration categories, β (SE), *p* value		
		Short: ≤6 h	Average: 7–8 h	Long: ≥9 h
PET-Aβ				
Global composite measure (FLR)	1	−0.15 (0.13), 0.259	Reference	−0.24 (0.27), 0.382
	2	−0.15 (0.14), 0.285	Reference	−0.24 (0.28), 0.385
PET-tau				
Entorhinal cortex	1	−0.09 (0.15), 0.544	Reference	0.18 (0.32), 0.573
	2	−0.05 (0.15), 0.716	Reference	0.26 (0.32), 0.404
Rhinal cortex	1	0.02 (0.16), 0.883	Reference	0.27 (0.35), 0.448
	2	0.02 (0.17), 0.918	Reference	0.32 (0.36), 0.378
Medial orbitofrontal gyrus	1	−0.13 (0.14), 0.357	Reference	0.28 (0.31), 0.366
	2	−0.13 (0.14), 0.359	Reference	0.37 (0.31), 0.232
Rostral anterior cingulate	1	−0.04 (0.14), 0.797	Reference	0.26 (0.30), 0.382
	2	−0.02 (0.14), 0.867	Reference	0.35 (0.30), 0.243
MRI				
Total brain volume, % of ICV	1	−0.004 (0.10), 0.966	Reference	−0.15 (0.14), 0.274
	2	0.05 (0.11), 0.620	Reference	−0.04 (0.15), 0.803
WMH, % of ICV	1	0.04 (0.06), 0.570	Reference	0.15 (0.09), 0.100
	2	0.03 (0.07), 0.609	Reference	0.17 (0.09), 0.077
WMH, extensive for age	1	1.20 (0.87–1.67), 0.504	Reference	1.13 (0.70–1.82), 0.910
	2	1.13 (0.77–1.66), 0.738	Reference	1.11 (0.66–1.88), 0.869
Covert brain infarcts	1	0.93 (0.54–1.60), 0.547	Reference	1.22 (0.67–2.22), 0.439
	2	1.05 (0.58–1.91), 0.707	Reference	1.39 (0.74–2.62), 0.343
Average FW	1	−0.004 (0.001), 0.790	Reference	0.006 (0.002), 0.003[a]
	2	−0.0002 (0.002), 0.891	Reference	0.003 (0.002), 0.138

Abbreviations: ATV(N) = amyloid tau vascular neurodegeneration; FLR = frontal, lateral, and retrosplenial cortices; FW = free-water; ICV = intracranial volume; WMH = white matter hyperintensity.
Model 1 was adjusted for age, sex, time between sleep assessment and neuroimaging, camera (PET sample only), and age squared (MRI sample only). Model 2 was additionally adjusted for *APOE4* allele carriers, depression, diabetes, hypertension, and prevalent cardiovascular disease. WMH was log-transformed.
[a] Significant findings at $p < 0.05$.

[0.003], $p = 0.124$), and short sleep was associated with higher FW fraction when adjusting for model 2 (β [SE] 0.007 [0.003], $p = 0.033$), with similar effect size for long sleep (β [SE] 0.006 [0.004], $p = 0.101$). This stratification highlights a potential U-shape association between sleep duration and higher FW fraction in depressed participants.

Longitudinal Analysis: Changes in Sleep Duration Categories and ATV(N) Neuroimaging Biomarkers

No significant associations between longitudinal changes in sleep duration categories and PET outcomes were observed (eTable 4, links.lww.com/WNL/D231). When looking at cerebrovascular MRI outcomes as compared with those with stable average sleep duration over time, many significant associations were observed with the 3 categories tending toward longer sleep over time (Table 3). Individuals going from average to long sleep duration over time had larger WMH volumes as compared with those with stable average sleep duration. Similarly, individuals going from short to long sleep duration over time had more extensive WMH for their age than those with stable average sleep duration (model 1 only). Individuals going from short or average sleep duration to long sleep duration over time had elevated average FW fraction compared with those with stable average sleep duration, which was also observed in those going from short to average sleep duration over time (model 2 only). On the other hand, those with stable long sleep duration over time had lower WMH volume and lower FW fraction than those with stable

Table 3 Longitudinal Changes in Sleep Duration Categories and MRI Outcomes

		Changes over time in sleep duration categories, β (SE), *p* value		
		Stable sleep duration over time		
MRI outcomes	Models	Stable short (n = 230)	Stable average (n = 1,114)	Stable long (n = 47)
Total brain volume, % ICV	1	−0.08 (0.13), 0.535	Reference	0.23 (0.28), 0.420
	2	0.04 (0.15), 0.781	Reference	0.30 (0.31), 0.334
WMH, % ICV	1	−0.01 (0.09), 0.885	Reference	−0.33 (0.18), 0.078
	2	−0.078 (0.10), 0.419	Reference	−0.43 (0.20), 0.028[a]
WMH, extensive for age	1	0.97 (0.58–1.60), 0.919	Reference	0.20 (0.03–1.51), 0.083
	2	0.73 (0.39–1.38), 0.971	Reference	NA
Covert brain infarcts	1	0.88 (0.42–1.85), 0.963	Reference	0.58 (0.13–2.56), 0.978
	2	0.80 (0.32–1.95), 0.972	Reference	0.73 (0.16–3.29), 0.975
Average FW	1	0.0016 (0.0021), 0.430	Reference	−0.0036 (0.0041), 0.383
	2	0.0016 (0.0023), 0.481	Reference	−0.019 (0.004), 0.020[a]
		Longer sleep duration over time		
		Short to average (n = 213)	**Average to long (n = 167)**	**Short to long (n = 14)**
Total brain volume, % ICV	1	−0.19 (0.14), 0.169	−0.28 (0.16), 0.073	−0.30 (0.50), 0.426
	2	−0.25 (0.16), 0.115	−0.19 (0.17), 0.278	0.10 (0.52), 0.853
WMH, % ICV	1	0.11 (0.09), 0.217	0.25 (0.10), 0.015[a]	0.51 (0.32), 0.118
	2	0.14 (0.10), 0.161	0.29 (0.11), 0.007[a]	0.61 (0.32), 0.059
WMH, extensive for age	1	1.15 (0.70–1.87), 0.616	1.29 (0.76–2.20), 0.375	3.50 (0.95–12.92), 0.040[a]
	2	1.31 (0.76–2.24), 0.950	1.33 (0.75–2.37), 0.950	3.74 (0.99–14.17), 0.914
Covert brain infarcts	1	0.82 (0.38–1.79), 0.965	1.31 (0.67–2.53), 0.948	1.64 (0.21–12.98), 0.940
	2	0.95 (0.41–2.21), 0.965	1.46 (0.72–2.97), 0.951	1.89 (0.23–15.28), 0.942
Average FW	1	0.004 (0.0021), 0.064	0.0088 (0.0024), 0.0002[a]	0.0213 (0.007), 0.003[a]
	2	0.0062 (0.0024), 0.009[a]	0.0083 (0.0022), 0.002[a]	0.0164 (0.0076), 0.031[a]
		Shorter sleep duration over time		
		Long to average (n = 87)	**Average to short (n = 281)**	**Long to short (n = 12)**
Total brain volume, % ICV	1	−0.13 (0.21), 0.543	0.01 (0.12), 0.912	−0.52 (0.54), 0.339
	2	0.10 (0.15), 0.781	0.02 (0.14), 0.866	−0.53 (0.53), 0.397
WMH, % ICV	1	−0.17 (0.13), 0.208	0.11 (0.08), 0.172	−0.52 (0.35), 0.134
	2	−0.17 (0.15), 0.269	0.17 (0.09), 0.056	−0.47 (0.39), 0.227
WMH, extensive for age	1	0.85 (0.39–1.82), 0.673	1.44 (0.96–2.15), 0.141	0.78 (0.09–6.45), 0.799
	2	0.74 (0.29–1.93), 0.970	1.55 (0.98–2.47), 0.944	1.01 (0.12–8.66), 0.959
Covert brain infarcts	1	0.59 (0.14–2.52), 0.978	0.91 (0.45–1.85), 0.961	NA
	2	0.37 (0.05–2.78), 0.998	1.21 (0.58–2.53), 0.957	NA
Average FW	1	0.0053 (0.0031), 0.082	−0.0003 (0.0019), 0.858	0.0017 (0.0087), 0.841
	2	0.0067 (0.0035), 0.058	0.0008 (0.002), 0.703	0.0019 (0.010), 0.849

Abbreviations: FW = free-water; ICV = intracranial volume; NA = nonapplicable because lack of event; OR = odds ratio; WMH = white matter hyperintensity. All categories were compared with the individuals with stable average sleep duration categories (7–8 hours) as reference (n = 1,114). Model 1 was adjusted for age, sex, time between sleep assessment and neuroimaging, and age squared. Model 2 was additionally adjusted for *APOE4* allele carriers, depression, diabetes, hypertension, and prevalent cardiovascular disease. WMH was log-transformed. Short sleep duration ≤6 hours, average sleep duration 7–8 hours, and long sleep duration ≥9 hours.
[a] Significant findings at $p < 0.05$.

Table 4 ATV(N) Neuroimaging Biomarkers With Longitudinal Continuous Changes in Sleep Duration

Outcomes	Models	β (SE), *p* value or OR (95% CI), *p* value			
		Increased by ≥2 h+ (vs 0 ± 1 h over time)	Decreased by ≥2 h+ (vs 0 ± 1 h over time)	Delta sleep duration increase	Delta sleep duration decrease
PET sample, N		17	24	185	196
PET-Aβ	1				
Global composite measure (FLR)		−0.27 (0.24), 0.257	−0.30 (0.21), 0.148	−0.14 (0.11), 0.176	−0.17 (0.08), 0.052
PET-tau	1				
Entorhinal cortex		0.01 (0.27), 0.963	0.19 (0.23), 0.406	0.09 (0.11), 0.379	0.09 (0.10), 0.359
Rhinal cortex		−0.21 (0.29), 0.479	−0.02 (0.25), 0.925	0.07 (0.12), 0.569	0.06 (0.10), 0.539
Medial orbitofrontal gyrus		−0.30 (0.26), 0.264	0.02 (0.22), 0.940	−0.01 (0.10), 0.911	−0.02 (0.09), 0.846
Rostral anterior cingulate		−0.29 (0.26), 0.267	0.11 (0.21), 0.619	−0.03 (0.10), 0.777	0.04 (0.09), 0.677
MRI sample, N		174	185	1,503	1,525
Total brain volume, % of ICV	1	−0.30 (0.15), 0.039[a]	−0.26 (0.14), 0.065	−0.11 (0.06), 0.064	−0.07 (0.06), 0.261
	2	−0.29 (0.16), 0.074	−0.21 (0.16), 0.186	−0.10 (0.07), 0.134	−0.04 (0.07), 0.562
WMH, % of ICV	1	0.14 (0.10), 0.145	−0.003 (0.094), 0.979	0.10 (0.04), 0.007[a]	0.03 (0.04), 0.484
	2	0.24 (0.10), 0.019[a]	0.047 (0.101), 0.639	0.12 (0.04), 0.003[a]	0.03 (0.04), 0.494
WMH, extensive for age	1	1.13 (0.67–1.89), 0.782	1.08 (0.66–1.77), 0.938	1.26 (1.02–1.55), 0.032[a]	1.13 (0.92–1.38), 0.237
	2	1.46 (0.85–2.51), 0.304	1.17 (0.68–2.03), 0.918	1.37 (1.10–1.72), 0.006[a]	1.17 (0.93–1.46), 0.182
Covert brain infarcts	1	1.31 (0.67–2.56), 0.551	1.10 (0.49–2.46), 0.923	1.27 (0.95–1.69), 0.102	1.12 (0.82–1.53), 0.487
	2	1.48 (0.72–3.05), 0.539	1.35 (0.59–3.07), 0.813	1.30 (0.95–1.79), 0.102	1.21 (0.87–1.67), 0.259
Average FW	1	0.0082 (0.0022), 0.0003[a]	0.0023 (0.0022), 0.297	0.002 (0.001), 0.031[a]	0.0004 (0.0009), 0.967
	2	0.0081 (0.0025), 0.001[a]	0.0027 (0.0025), 0.276	0.002 (0.001), 0.021[a]	0.0005 (0.0010), 0.600

Abbreviations: ATV(N) = amyloid tau vascular neurodegeneration; FLR = frontal, lateral, and retrosplenial cortices; FW = free-water; ICV = intracranial volume; WMH = white matter hyperintensity.
Increased and decreased sleep duration by 2 hours or more were compared with participants within an hour of sleep duration change over time in either direction. Delta sleep duration changes were treated continuously in 2 groups: (1) those whose sleep duration did not change or increased over time and (2) those whose sleep duration did not change or decreased over time. Model 1 was adjusted for age, sex, time between sleep assessment and neuroimaging, camera (PET sample only), and age squared (MRI sample only). Model 2 was additionally adjusted for *APOE4* allele carriers, depression, diabetes, hypertension, and prevalent cardiovascular disease. WMH was log-transformed.
[a] Significant findings at $p < 0.05$.

average sleep duration (model 2 only). No association between changes in sleep duration categories tending toward shorter sleep duration or stable short sleep duration over time was observed with MRI outcomes.

Longitudinal Analysis: Changes in Continuous Sleep Duration and ATV(N) Neuroimaging Biomarkers

Individuals who reported their sleep to increase by ≥2 hours over time had lower total brain volume (model 1 only), higher WMH volume (model 2 only), and higher average FW fraction as compared with those who self-reported that their sleep duration changed only by an hour or less in either direction (Table 4). Continuous increase in sleep duration (continuous delta value, follow-up minus baseline) over time was associated with larger WMH volume, higher prevalence of WMH extensive for age, and higher average FW fraction. No associations were observed with changes in sleep duration toward shorter sleep and ATV(N) neuroimaging biomarkers, and no association was observed with PET outcomes.

Because the PET sample was younger than the MRI sample, we explored whether the findings between delta increased sleep duration over time and MRI outcomes were still observed when considering only participants younger than 65 years. Increase in sleep duration over time was still associated with higher WMH volume and WMH extensive for age (β = 0.15, $p = 0.015$; OR = 1.37, $p = 0.29$) whereas higher average FW was no longer significant (β = 0.0008, $p = 0.506$).

Discussion

In this longitudinal community-based cohort, we observed that an increase of self-reported sleep duration over time was

associated with neuroimaging biomarkers of vascular brain injury, namely higher WMH burden and FW fraction. WMH are well-known markers of small vessel disease and have been identified as AD risk factors.[21] FW fraction is a novel measure inferring on unrestricted extracellular water and is associated with ischemic vasogenic edema.[20] FW fraction is elevated in patients with MCI and dementia[22] and associated with poorer cognitive function and dementia progression.[23]

To our knowledge, only 1 previous study explored the association between longitudinal changes in sleep duration over time and multiple ATV(N) neuroimaging biomarkers. In participants aged 42 years on average at baseline, repeated assessments of self-reported sleep duration over 28 years did not reveal associations with gray matter volumes or white matter diffusion measurements, although only slight variations in sleep duration were detected in their sample over time.[24] The importance of longer sleep duration over time, as compared with shorter sleep duration over time, has been highlighted before. While both shortening and lengthening of sleep duration over time are associated with higher risk of developing MCI, higher ORs were observed for sleep duration that lengthened by 2 hours or more.[4] Consistently, we have observed lower total brain volume suggestive of neurodegeneration only when extensive longer sleep duration over time was observed (2 hours or more). Our findings might be reflective of the sensitivity of longer sleep duration over time to early cerebrovascular changes, as compared with any single time point measurement, especially given the younger age of our participants.

A few previous studies explored the association between cross-sectional sleep duration and MRI biomarkers of cerebrovascular pathology and neurodegeneration, with mixed results. Whereas long sleep duration was associated with higher WMH burden,[25] reporting both short and long sleep duration in older women was associated with subsequent higher FW values.[26] Short sleep duration, rather than longer sleep, seems more consistently associated with atrophy.[27,28] In cognitively healthy participants, baseline short and long sleep duration were associated with subsequent atrophy rates over frontal and temporal regions.[29] Part of the mixed results observed previously with cerebrovascular neuroimaging biomarkers might be due to different sleep duration trajectories. In this study, we observed that transitioning to longer sleep duration over time was associated with a detrimental pattern of higher WMH volume and FW fraction, whereas those with consistently long sleep duration over time showed the opposite pattern (Table 3). Stable long sleep duration might be an individual trait kept through life, potentially driven by good sleep hygiene habits, cognitively and physically demanding daytime activities, and genetics that could have beneficial impacts on the brain. On the other hand, transitioning to longer sleep over time might be more representative of pathologic processes. Because those with stable long sleep duration vs those with longer sleep duration over time will inevitably report a similar sleep length at some point, this can easily lead to mixed results in cross-sectional models that cannot differentiate between these 2 trajectories.

Mixed results were also found between self-reported sleep duration and PET outcomes, with studies finding higher Aβ or tau burden with short sleep duration[30-33] or long sleep duration,[34] whereas other reported no associations.[35-37] In our cohort, the younger age of our PET sample might explain the lack of association between Aβ and tau burden with sleep duration. Overall, we hypothesized that differences observed between studies might be mostly age-based and stage-based, meaning that different findings between self-reported sleep duration and ATV(N) neuroimaging biomarkers might differ depending on where a participant is on the AD trajectory.

The first hypothesis potentially explaining our result is that longer sleep duration over time may promote vascular pathology. Cerebrovascular pathology is highly prevalent in the AD trajectory and is central to vascular dementia etiology.[6,7] In a study using neuroimaging modeling, vascular changes were more likely to precede and trigger other pathologic changes in the course of late-onset sporadic AD, such as amyloid, neuronal function, metabolism, structural changes, and cognitive changes.[38] We found no association with covert brain infarcts, which might be because of the relatively young age of our cohort, putting them earlier in the pathologic trajectory. It remains unclear however how longer sleep duration may promote vascular pathology. Cerebrovascular neuroimaging biomarkers are closely linked to neuroinflammatory processes,[39,40] which are also of great significance in the development of AD. Long sleep duration was previously shown to associate with elevated inflammatory levels.[41] Long sleep duration is also associated with the subsequent incidence of multiple vascular and metabolic diseases, such as diabetes, cardiovascular diseases, obesity, and stroke[42] and vascular processes such as arterial stiffness and higher blood pressure variability,[43] which might support its association with cerebrovascular neuroimaging biomarkers in this study. Other hypotheses that have been formulated to explain health risks associated with sleeping longer include circadian dysfunctions that could result from sleeping longer and lack of beneficial daytime challenges and mild stressors.[44] In fact, increasing self-reported sleep duration over time might underlie poorer sleep quality (changes in sleep architecture with less slow-wave sleep, sleep fragmentation) and thus a perception of longer sleep and longer time in bed.[44]

The alternative hypothesis explaining our findings is that cerebrovascular pathology may promote longer sleep duration over time. As we sought to understand how changes in sleep duration may be associated with subsequent ATV(N) neuroimaging biomarkers in the brain, our design included sleep duration changes before the assessment of PET and MRI outcomes. However, we cannot exclude that cerebrovascular pathology observed at follow-up might have been already in place during the period where we observed change in sleep duration. Longer sleep duration is often believed to be a marker of ongoing neurodegenerative processes.[2] On one

hand, longer sleep duration over time may be representative of damage to wake-promoting structures because longer sleep in patients with AD has been associated with postmortem nuclei damage.[45] On the other hand, longer sleep duration might be a compensatory response to vascular pathology. One of the most compelling evidence of compensation comes from an experimental protocol, where sleep was extended for 5 continuous nights (approximately 2-hour extension on average). This experiment resulted in higher peak forearm vascular conductance and total excess blood flow, representing increased vasodilatory capacity of the peripheral microvasculature, rather than impairment of vascular function.[46] This suggests that a compensatory increase in sleep duration might contribute to fight vascular dysregulation.

Other confounders or mediators are a common explanation formulated when long sleep duration is found in association with poorer health outcomes. In this study, we adjusted for multiple potential confounders and mediators. Normal aging is generally associated with a reduction in self-reported sleep duration (approximately 10 minutes every decade) rather than longer sleep duration,[47] the latter being observed mostly in the context of pathologic conditions.[42] In addition, underlying undiagnosed sleep disorders such as obstructive sleep apnea or undiagnosed depression might cause longer sleep duration over time and cerebrovascular pathology.[44] However, although obstructive sleep apnea is believed to contribute to cognitive impairment and dementia risk,[48,49] we showed previously in a subsample of the Offspring cohort that the apnea-hypopnea index was not correlated with self-reported sleep duration, whereas it was correlated with shorter objective sleep duration.[50] This suggests that obstructive sleep apnea is unlikely to result in the portrait of longer self-reported sleep duration observed here.

Strengths of this study included our large community-based sample followed longitudinally, which allowed to explore changes in sleep duration because a large sample is required to investigate the multiple sleep duration changes trajectories. Although self-reported sleep measurements have their importance and represent sleep habits, they are limited by the fact that many people do not adequately report their sleep, and thus, future studies should evaluate longitudinal changes in sleep quantity using objective measure and their association with ATV(N) biomarkers. Another limitation is the racial composition of the FHS Offspring cohort, which mostly included White participants.

We concomitantly investigated ATV(N) neuroimaging biomarkers in association with self-reported changes in sleep duration. Vascular pathology in the brain as evidenced by higher WMH burden and FW fraction was associated with self-reported sleep duration that became longer over time in our large community-based cohort. Longer sleep duration over time may be an early change in the AD trajectory but whether it could subsequently provoke Aβ or tau pathology remains unclear, despite the previous association between AD risk and longer sleep duration over time.[2-4] Future studies are necessary to understand the directionality of this association to inform whether preventing longer sleep duration over time could be beneficial or detrimental to brain health.

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