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Authors

Baril, Andrée-Ann

Beiser, Alexa S

DeCarli, Charles

et al.

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ORIGINAL ARTICLE

Self-reported sleepiness associates with greater brain and cortical volume and lower prevalence of ischemic covert brain infarcts in a community sample

Andrée-Ann Baril[1,2,*], Alexa S. Beiser[1,3,4], Charles DeCarli[5], Dibya Himali[1], Erlan Sanchez[6], Marina Cavuoto[7], Susan Redline[8,9], Daniel J. Gottlieb[8,9,10], Sudha Seshadri[1,3,11], Matthew P. Pase[1,7,12,*] and Jayandra J. Himali[1,3,4,11,13,*]

[1]The Framingham Heart Study, Framingham, MA, USA, [2]Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada, [3]Department of Neurology, Boston University School of Medicine, Boston, MA, USA, [4]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA, [5]Department of Neurology, University of California, Davis, CA, USA, [6]Sunnybrook Research Institute, University of Toronto, Toronto, ON, Canada, [7]Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, VIC, Australia, [8]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, MA, USA, [9]Division of Sleep Medicine, Harvard Medical School, Boston, MA, USA, [10]VA Boston Healthcare System, Boston, MA, USA, [11]Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio, TX, USA, [12]Harvard T.H. Chan School of Public Health, MA, USA and [13]Department of Population Health Sciences, University of Texas Health Science Center, San Antonio, TX, USA

*Corresponding author. Andrée-Ann Baril, Douglas Mental Health University Institute, Pavillon Perry, 6875 Boulevard LaSalle, Montréal, QC, H4H 1R3, Canada. Email: andree-ann.baril@mcgill.ca | baril.andreeann@gmail.com. Jayandra Jung Himali, Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, 7703 Floyd Curl Drive, Mail Code 8070, University of Texas Health Science Center, San Antonio, TX, 78229-3900, USA. Email: himali@uthscsa.edu.

The work was performed at the Framingham Heart Study.
*These authors contributed equally to the manuscript.

Abstract

Study Objectives: We evaluated if self-reported sleepiness was associated with neuroimaging markers of brain aging and ischemic damage in a large community-based sample.

Methods: Participants from the Framingham Heart Study Offspring cohort (n = 468, 62.5 ± 8.7 years old, 49.6%M) free of dementia, stroke, and neurological diseases, completed sleep questionnaires and polysomnography followed by magnetic resonance imaging (MRI), 3 years later on average. We used linear and logistic regression models to evaluate the associations between Epworth Sleepiness Scale (ESS) scores and total brain, cortical and subcortical gray matter, and white matter hyperintensities volumes, and the presence of covert brain infarcts.

Results: Higher sleepiness scores were associated with larger total brain volume, greater cortical gray matter volume, and a lower prevalence of covert brain infarcts, even when adjusting for a large array of potential confounders, including demographics, sleep profiles and disorders, organic health diseases, and proxies for daytime cognitive and physical activities. Interactions indicated that more sleepiness was associated with larger cortical gray matter volume in men only and in *APOE* ε4 noncarriers, whereas a trend for smaller cortical gray matter volume was observed in carriers. In longitudinal analyses, those with stable excessive daytime sleepiness over time had greater total brain and cortical gray matter volumes, whereas baseline sleepiness scores were not associated with subsequent atrophy or cognitive decline.

Conclusion: Our findings suggest that sleepiness is not necessarily a marker of poor brain health when not explained by diseases or sleep debt and sleep disorders. Rather, sleepiness could be a marker of preserved sleep-regulatory processes and brain health in some cases.

Statement of Significance

Self-reported sleepiness has been observed as a consequence of many sleep disorders and health conditions, such as dementia and stroke. However, the association of daytime sleepiness with markers of brain aging and ischemic damage remains unclear when it is independent of sleep disorders, sleep debt, or diseases. Here, we show that higher levels of self-reported daytime sleepiness were associated with greater total brain and cortical gray matter volumes as well as lower risk of presenting covert brain infarcts, when adjusting for a large array of confounders (e.g. sleep disorders and habitual sleep patterns, cardiovascular risk factors, and depression). Our findings challenge the view that daytime sleepiness is a marker of poorer brain health when it is not explained by another pathology or sleep disorder.

Key words: sleep propensity; magnetic resonance imaging; stroke; infarcts; gray matter; cortex; alzheimer's disease; dementia; apolipoprotein E; sex

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Introduction

Sleep disturbances are an increasing public health concern [1], with daytime sleepiness being one of the most important consequences, especially as it is present in up to a third of adults [2]. Excessive daytime sleepiness is associated with several negative outcomes, such as mortality, multiple diseases, poor work performance, and road accidents [2–4]. Daytime sleepiness can be conceptualized as an increased sleep drive and reduced wake drive [5], encompassing several factors, including alertness, drowsiness, sleep propensity, as well as sleep debt, and need [6]. In addition to being a common consequence of sleep disorders, such as obstructive sleep apnea, insomnia, hypersomnia, or narcolepsy, sleepiness is often observed as a symptom of several organic health diseases, including type 2 diabetes, depression, epilepsy, and Parkinson's Disease [7–10]. In fact, sleepiness has been reported in participants with dementia or stroke [11–13], and also as a risk factor for the development of these neurological conditions [14–17]. Therefore, in addition of being a consequence of poor sleep, sleepiness could also be the result of neurodegenerative processes and accelerated brain aging [10, 18], where the breakdown of important sleep and wake regulatory cerebral circuits could manifest as daytime sleepiness. In fact, some studies have shown that the level of sleepiness and the presence of excessive daytime sleepiness were associated with brain atrophy, although this association was partially explained by sleep disturbances [18, 19]. However, daytime sleepiness can also arise independent of sleep disorders and health conditions [2, 20], and it remains unclear how sleepiness itself associates with markers of brain aging and ischemic damage.

To better understand the neuroanatomical correlates of daytime sleepiness in the older population, we evaluated if self-reported sleepiness was associated with MRI markers of brain aging and ischemic damage, while accounting for several confounding factors such as sleep characteristics and medical conditions.

Methods

Sample selection in the Framingham Heart Study

The Framingham Heart Study is a large multigenerational cohort study in which participants were regularly examined approximately every 4 years. Between 1995 and 1998 at their sixth clinical examination, a subset of participants from the Framingham Heart Study Offspring cohort [21] were included in the Sleep Heart Health Study, which included sleep questionnaires and in-home polysomnography (PSG). Subsequently, participants were invited to undergo brain MRI and cognitive testing at their seventh clinical examination between 1999 and 2002. From the 542 available participants with a sleep assessment and MRI, we excluded those with neurological diseases, including dementia and stroke (n = 20); those aged <40 years old (n = 6) to evaluate MRI markers of brain aging and ischemic damage in middle-aged and elderly participants; and those with unsatisfactory sleep data for scoring (n = 29). Of the remaining 487 participants, 468 completed the ESS, which represented our final sample for all analyses exploring sleepiness. All participants gave their written informed consent before the beginning of the study. The institutional review board at Boston University Medical Center approved the study.

Daytime sleepiness and sleep assessments

The evening of their in-home PSG, participants completed the ESS and answered questions about their habitual sleep duration and latency, insomnia symptoms, and nap frequency and duration. The ESS is the most commonly used questionnaire to assess self-reported sleepiness, which measures sleep propensity and drowsiness [22]. The ESS score was treated continuously, as well as dichotomously to assess excessive daytime sleepiness (ESS > 10).

Some self-reported sleep characteristics were investigated as covariates. Habitual sleep duration was coded ordinally. Insomnia symptoms were composed of five Likert-type questions and combined as a single severity score published by our group previously [23], assessing difficulty falling and maintaining sleep, waking up too early, feeling unrested, and not getting enough sleep. Nap frequency per week was coded as a 3-level variable: no naps; 1–3 naps a week; 4+ naps a week. Nap duration was also coded similarly: no naps; 1–20 min naps; and 25 min+ naps.

The in-home PSG procedure and scoring criteria were described previously [24–26]. Briefly, the PSG included electroencephalograms (C3/A1, C4/A2), electrooculograms, electrocardiogram, chin electromyogram, oximetry, chest wall and abdomen inductance plethysomnography, and nasal/oral airflow. We extracted objective sleep parameters that could be linked to daytime sleepiness and/or confounding to the association between ESS scores and MRI metrics, including the obstructive apnea-hypopnea index (AHI), sleep efficiency, and wake after sleep onset (WASO), total sleep time, and sleep stages.

MRI markers of brain aging and ischemic damage

MRI metrics were measured using a brain-dedicated Siemens Magnetom MRI (1.5T) with parameters and sequences described previously [27]. MRI images were processed using an atlas-based method [28], and the volumetric segmentation of the total brain, cortical, and subcortical gray matter, as well as white matter hyperintensities was performed from FLAIR and T1-weighted images by automated procedures previously described with high inter-rater reliability [27, 29–31]. Volumes were computed as a percentage of the total intracranial volume to remove any effect of head size. In addition to white matter hyperintensity volume as a marker of ischemic damage, covert brain infarcts were inspected visually by three raters to uncover lesions ≥3 mm [27] and were coded according to their presence or absence.

Global cognitive assessment

Participants were invited to undergo a neuropsychological assessment at their seventh clinical examination, which was described previously [32]. Using all tests, a weighted composite global measure of cognitive function was derived using principal component analysis forcing a single factor solution as described previously [33]. Briefly, tests from the neuropsychological battery were Visual Reproductions Immediate and Delayed Recall, Logical Memory Immediate and Delayed Recall, Similarities, Trail Making Test B, Paired Associate Learning Immediate and Delayed Recall, and Hooper Visual Organization Test. Collectively, these tests assessed verbal and visual memory, learning, attention, abstract reasoning, language, visuoperceptual organization,

psychomotor speed, and premorbid intelligence [32]. All scores were coded such that higher scores represent better cognitive performance.

Clinical covariates

Covariates were assessed concomitantly with the sleep assessment at participants' sixth clinical examination. To assess the presence of the *apolipoprotein E ε4* (*APOE ε4*) allele, the two polymorphic sites of the *APOE* gene were genotyped from whole blood, amplified by PCR for 35 cycles (DNA Thermal Cycler, PTC-100, MJ Research), and separated by electrophoresis. Participants were classified according to their *APOE ε4* allele carrier status: at least one ε4 allele for carriers and no ε4 allele for non-carriers. The presence of depressive symptoms was defined as Center for Epidemiologic Studies Depression Scale ≥16 [34], self-reported depression diagnosis, and/or current antidepressant usage. The use of sleeping medications was self-reported, with regular usage defined as at least 1 day per week. Body mass index was calculated from each participants' height and weight measured at the clinical examination.

The Revised Framingham Stroke Risk Profile score, a clinical risk prediction tool for the 10-year risk of incident stroke, was assessed using clinical information, including age, smoking status, prevalent cardiovascular diseases, atrial fibrillation, diabetes mellitus, and hypertension [35]. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose ≥126 mg/dL or use of oral hypoglycemic agents or insulin. Current smoking was determined by self-report with at least one cigarette per day within the year classifying a participant as an active smoker. Prevalent cardiovascular disease was defined as coronary heart disease, peripheral arterial disease, and/or heart failure.

Education was coded as a 4-level variable: no high school degree; high school degree; some college education; and college graduate. As a marker of premorbid functioning, the Wide Range Achievement Test (WRAT) score was assessed. The number of cups of regular coffee on a regular day was self-reported and treated continuously. The Physical Activity Index was calculated from self-reported descriptions by participants of their physical activity habits (type of employment, walks, stairs, exercise, time sitting versus standing, and housework).

Statistical Analyses

Statistical analyses were performed using SAS software V9.4 (SAS Institute Cary, NC). To achieve normality and reduce the impact of outliers, natural log transformations were applied to the ESS scores, the obstructive AHI, WASO, white matter hyperintensities volume, and body mass index. A correlation matrix between ESS scores and other self-reported and PSG sleep characteristics were calculated, using Pearson's correlations when variables were normally distributed and symmetrically and Spearman's correlations when they were not. Participants with missing data were removed on an analysis-by-analysis basis. Results were considered significant if $p < .05$, except for interactions that were considered significant at $p < .1$ since they are generally less powerful than main effects.

Primary analysis We used multivariable linear and logistic regression models to evaluate the association between ESS scores standardized to the mean as a continuous variable as well as dichotomous ESS (>10 to assess excessive daytime sleepiness compared to the rest of the sample) with each MRI metric. Models included the following covariates: age, age squared (given the non-linear association between age and MRI characteristics), sex, the time interval between the sleep assessment and MRI, *APOE ε4* allele carrier status, body mass index, regular usage of sleeping pills, depressive symptoms, and Revised Framingham Stroke Risk Profile scores. These covariates were selected a priori to account for conditions that could affect brain aging and ischemic damage or have the potential to provoke sleepiness.

Secondary analyses In order to better understand how self-reported sleepiness as measured by the ESS is associated with MRI markers of brain aging and ischemic damage, we performed a series of sensitivity analyses.

Additional covariates: We added specific covariates to the significant primary statistical models between continuous ESS scores and MRI metrics in order to clarify whether they accounted for our findings. These were added in separate models, as they could have led to over-adjusting and collinearity in a single model. These were: (1) the obstructive AHI, since sleepiness is a common symptom of obstructive sleep apnea; (2) insomnia symptoms combined as a single severity score, as insomnia could be associated with different patterns of daytime sleepiness; (3) habitual self-reported sleep duration, in order to adjust for potential habitual sleep debt or hypersomnia; (4) nap frequency per week and nap duration, since naps are related to both daytime sleep propensity and sleep debt; (5) regular coffee intake, since self-reported levels of sleepiness may be confounded by caffeine; (6) education, as a marker of cognitive reserve, and potentially, as a proxy for daytime mental load; (7) the WRAT score, as a marker of premorbid functioning, also as a proxy for cognitive reserve and daytime mental load; and (8) the Physical Activity Index, as a marker of daytime physical energy expenditure.

Interactions: In order to explore whether the association between the ESS and MRI metrics was modified by individual factors that could potentially be changing how daytime sleepiness is expressed and/or is associated with MRI markers, we performed a series of linear and logistic regression models while including an interaction term. The interaction variables included the *APOE ε4* allele carrier status—the strongest genetic factor for late onset Alzheimer's Disease [36, 37], age with a cutoff of 60 years old, and sex. Although other demographic variables and conditions were considered, they were not selected for interactions testing because of their low proportion in our sample (see Table 1). When interactions were significant at $p < .1$, we stratified the models by the interaction variables. Interactions models included as covariates: age, age squared, sex (except for when sex is considered as a moderator), and time between the sleep assessment and MRI.

Global cognition and ESS: In order to evaluate whether the association between the ESS scores and MRI metrics translates to cognitive functioning, we explored the relationship between the ESS scores and global cognition using the

Table 1. Demographic, clinical, and sleep characteristics of the sample

Characteristics (n = 468)	Mean (standard deviation) or n (%)
Age at sleep evaluation, years	58.6 (8.8)
Age at MRI, years	62.5 (8.7)
Time between sleep and MRI, years	3.3 (1.0)
Sex, men, n (%)	232 (49.6)
Education, n (%)	
No high school degree	18 (3.9)
High school degree	136 (29.1)
Some college education	149 (31.8)
College graduate	165 (35.3)
Clinical covariates	
Apolipoprotein E ε4allele carrier, n (%)	99 (21.6)
Depression symptoms, n (%)	54 (11.5)
Systolic blood pressure, mmHg	125.8 (17.2)
Treated for hypertension, n (%)	105 (22.5)
Framingham Stroke Risk Profile score, score units	0.03 (0.04)
Body mass index, kg/m^2	28.0 (4.8)
Diabetes mellitus, n (%)	43 (9.2)
Current smoking, n (%)	65 (13.9)
Prevalent cardiovascular disease, n (%)	29 (6.2)
PSG sleep parameters	
Total sleep time, h	6.3 (1.0)
Sleep latency, min	22.3 (23.1)
Sleep efficiency, %	83.1 (9.8)
N1 sleep stage, %	4.9 (3.4)
N2 sleep stage, %	55.6 (11.3)
N3 sleep stage, %	18.5 (10.9)
REM sleep stage, %	21.0 (6.0)
WASO, min	56.1 (40.3)
AHI, events/h	8.8 (12.9)
Moderate OSA, AHI 15–30, n (%)	80 (19.0)
Severe OSA, AHI >30, n (%)	23 (5.5)
Self-reported sleep parameters	
Self-reported habitual sleep duration, h	7.0 (1.1)
Self-reported habitual sleep latency, min	15.7 (15.4)
Insomnia symptoms score, score units/20	7.7 (3.9)
Epworth Sleepiness Scale, score units/24	6.9 (4.1)
Excessive daytime sleepiness, ESS > 10, n (%)	86 (18.5)
Habitual nap frequency, # per week	2.1 (3.5)
Habitual nap duration, min per week	5.7 (18.6)
Regular usage of sleeping pills, n (%)	85 (18.4)
Coffee intake, # per day	2.0 (2.2)
MRI metrics	
Total brain volume, % of ICV	77.5 (2.4)
Cortical gray matter volume, % of ICV	37.4 (1.7)
Subcortical gray matter volume, % of ICV	3.1 (0.3)
White matter hyperintentisites, % of ICV	0.08 (0.22)
Covert brain infarcts present, n (%)	46 (9.8)

AHI, Apnea-Hypopnea Index; ICV, intracranial volume; OSA, obstructive sleep apnea; WASO, wake after sleep onset.

composite neuropsychological measure (n = 491). We included the same covariates as in our primary analyses with the addition of education, as well as a second model further adjusting for the AHI.

Longitudinal analyses: After 5.2 (0.3) years on average (range from 4.8 to 7.1 years), 341 participants completed the ESS for a second time. In order to evaluate whether changes in sleepiness levels were associated with MRI metrics and the neuropsychological composite score, the annualized change in ESS scores was entered as the predictor in regression models, using the same covariates as the primary analysis. Of note, the MRI and neuropsychological testing fell in-between both ESS completion for most participants. Four groups were created based on ESS score changes. Selected MRI metrics (total brain volume, cortical gray matter volume) were compared across these groupings: (1) Stable nonsleepy (ESS ≤ 10 at both time points, 74%); (2) Stable excessive daytime sleepiness (ESS > 10 at both time points, 13%); (3) Developed excessive daytime sleepiness (ESS ≤10 at baseline and >10 at follow-up, 6%); and (4) Resolved excessive daytime sleepiness (ESS > 10 at baseline and ≤10 at follow-up, 7%).

After 6.7 (0.9) years on average (range from 3.5 to 9.8 years), 373 participants had a repeat brain MRI scan. After 6.7 (0.9) years on average (range from 2.7 to 10.2 years), 422 participants had repeat neuropsychological testing. To evaluate whether sleepiness levels were associated with atrophy and cognitive decline, continuous ESS scores were entered in linear regression models in association with subsequent annualized change in total brain volume, cortical gray matter volume, and global cognitive composite score, adjusted for primary covariates (+ education when considering cognition).

Results

Sample characteristics

The sample included participants aged between 41 and 81 years at the time of the sleep assessment (45–84 years at the time of the MRI), with almost equal proportions of men and women. Characteristics of the sample are presented in Table 1. Overall, 18.5% presented with excessive daytime sleepiness (ESS > 10) in our sample, which is similar to the prevalence in the general community as reported previously in the same age group (between 11.4% and 27.3%) [38–41]. The time between the sleep assessment and the MRI was 3 years in average, ranging from 1.5 to 7.4 years. Less than 15% of the sample presented with depressive symptoms, diabetes, smoking, cardiovascular diseases, or severe obstructive sleep apnea.

More sleepiness as evidenced by higher ESS scores correlated with higher nap frequency and a higher proportion of N2 sleep to the detriment of N3 sleep (Table 2). Other self-reported sleep measures correlated more with objective PSG variables than the ESS scores correlated with PSG variables: The number of self-reported naps per week correlated with short sleep duration, longer sleep latency, and WASO, lower sleep efficiency, higher AHI, as well as a higher proportion of N2 sleep to the detriment of N3 sleep. Longer self-reported sleep latency correlated with longer objective sleep latency, shorter sleep duration, lower sleep efficiency, and longer WASO.

Primary analysis: associations between ESS scores and MRI metrics

A higher ESS score, representing more self-reported daytime sleepiness, was significantly associated with a higher total brain volume, higher cortical gray matter volume, and lower risk of presenting covert brain infarcts (Table 3). When looking

Table 2. Correlation matrix between the ESS score and other sleep characteristics

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Self-reported sleep parameters												
1) ESS												
2) #naps/week	.449											
	<.001											
3) Latency	−.078	.030										
	.095	.529										
4) Duration	−.015	.017	−.206									
	.755	.712	**<.001**									
PSG sleep parameters												
5) Duration	.063	−.149	−.179	.229								
	.237	**.006**	**<.001**	**<.001**								
6) Latency	−.090	.142	.206	−.043	−.442							
	.136	**.016**	**<.001**	.468	**<.001**							
7) Efficiency	.074	−.160	−.269	.036	.707	−.586						
	.209	**.006**	**<.001**	.537	**<.001**	**<.001**						
8) WASO	−.061	.096	.189	.072	−.349	.148	−.823					
	.185	**.040**	**<.001**	.126	**<.001**	**.011**	**<.001**					
9) AHI	.066	.115	.012	−.009	−.219	.064	−.170	.151				
	.170	**.017**	.797	.856	**<.001**	.292	**.005**	**.002**				
10)%N1	−.031	.060	.081	.003	−.051	.021	−.271	.368	.069			
	.501	.204	.083	.958	.345	.718	**<.001**	**<.001**	.147			
11)%N2	.187	.148	−.042	.012	−.044	−.002	−.093	.118	.195	.096		
	<.001	**.002**	.369	.807	.411	.971	.111	**.011**	**<.001**	**.038**		
12)%N3	−.152	−.137	.055	−.042	−.056	.049	.055	−.133	−.147	−.402	−.812	
	.001	**.003**	.241	.372	.296	.403	.345	**.004**	**.002**	**<.001**	**<.001**	
13)%REM	−.045	−.034	−.066	.052	.203	−.034	.212	−.155	−.137	−.012	−.456	−.062
	.335	.476	.158	.267	**<.001**	.109	**<.001**	**<.001**	**.004**	.777	**<.001**	.185

R values are represented in the first row of each correlation while *p*-values are presented on the second row. Bold values represent significant associations. Spearman correlations were used when variables were not normally distributed or symmetrically, and Pearson correlations were used otherwise. AHI, Apnea-Hypopnea Index; ESS, Epworth Sleepiness Scale; PSG, polysomnography; REM, rapid-eye movement; WASO, wake after sleep onset.

Table 3. Associations between self-reported daytime sleepiness with MRI metrics

	β	*SE*	*p*
Total brain volume, % ICV			
Continuous ESS scores	0.328	0.137	**.017**
Excessive daytime sleepiness (ESS > 10)	0.606	0.221	**.006**
Cortical gray matter volume, % ICV			
Continuous ESS scores	0.254	0.119	**.033**
Excessive daytime sleepiness (ESS > 10)	0.484	0.193	**.013**
Subcortical gray matter volume, % ICV			
Continuous ESS scores	−0.009	0.023	.696
Excessive daytime sleepiness (ESS > 10)	−0.019	0.037	.613
White matter hyperintensities volume, % ICV			
Continuous ESS scores	0.005	0.070	.942
Excessive daytime sleepiness (ESS > 10)	−0.054	0.110	.626
	OR	95% CI	*p*
Covert brain infarcts, (presence/absence)			
Continuous ESS scores	0.579	0.358-0.937	**.026**
Excessive daytime sleepiness (ESS > 10)	0.677	0.285-1.609	.378

A natural log transformation was applied to ESS and white matter hyperintensities volume. Dichotomous ESS scores was cutoff at >10, representing excessive daytime sleepiness compared to those without. Bold values represent significant associations. MRI metrics are presented as a percentage of intracranial volume, except for covert brain infarcts. Models were adjusted for age, age squared, sex, and time between ESS and MRI assessments, *APOE* ε4 allele carriers, body mass index, sleeping medications, depression, and revised Framingham Stroke Risk Profile score. CI, confidence interval; ESS, Epworth Sleepiness Scale; ICV, intracranial volume; MRI, magnetic resonance imaging; OR, Odds ratio; SE, standard error.

at excessive daytime sleepiness characterized by an ESS score >10, these participants had higher total brain volume and cortical gray matter volume compared to those without excessive daytime sleepiness. No associations were observed between the ESS score and subcortical gray matter volume or white matter hyperintensities volume.

Secondary analysis: additional covariates

The primary results between continuous ESS scores and MRI metrics (total brain volume, cortical gray matter volume, covert brain infarcts) remained similar after including additional adjustments for the AHI, insomnia symptoms, habitual self-reported sleep duration, nap frequency and duration, education or WRAT scores (Table 4). Some associations were now observed at a trend level, although effect sizes were similar to the primary analyses.

When adjusting significant associations between MRI metrics and continuous ESS scores for coffee intake or physical activity levels, findings were rendered non-significant with lower effect sizes (Table 4). However, results remained significant with the dichotomous ESS when adjusting for coffee intake (total brain volume, β, *SE*: 0.584, 0.220, $p = .008$; cortical gray matter volume, β, *SE*: 0.469, 0.193, $p = .015$) and physical activity levels (total brain volume, β, *SE*: 0.661, 0.225, $p = .004$; cortical gray matter volume, β, *SE*: 0.592, 0.166, $p = .003$) with similar or even higher effect sizes, suggesting a threshold effect when adjusting by these factors.

Table 4. Additional statistical adjustments in the association between continuous ESS scores and significant MRI metrics

Regressions with continuous ESS scores, additionally adjusted for:	Total brain volume, % ICV		Cortical gray matter volume, % ICV		Covert brain infarcts, (presence/absence)	
	β (SE)	*p*	β (SE)	*p*	OR (95% CI)	*p*
AHI	0.361 (0.140)	**.010**	0.273 (0.124)	**.029**	0.656 (0.398–1.082)	.099
Insomnia severity	0.327 (0.140)	**.020**	0.239 (0.121)	.050	0.574 (0.353–0.934)	**.025**
Habitual sleep duration	0.306 (0.139)	**.028**	0.213 (0.120)	.076	0.536 (0.330–0.871)	**.012**
Coffee intake	0.106 (0.071)	.134	0.070 (0.062)	.263	0.955 (0.776–1.175)	.665
Nap frequency	0.330 (0.154)	**.033**	0.345 (0.134)	**.010**	0.555 (0.310–0.995)	**.048**
Nap duration	0.341 (0.144)	**.018**	0.295 (0.125)	**.019**	0.550 (0.331–0.913)	**.021**
Education	0.330 (0.137)	**.016**	0.251 (0.119)	**.035**	0.574 (0.355–0.929)	**.024**
WRAT score	0.323 (0.138)	**.020**	0.254 (0.120)	**.034**	0.617 (0.376–1.013)	.056
Physical activity index	0.114 (0.071)	.110	0.086 (0.062)	.169	0.961 (0.776–1.189)	.712

A natural log transformation was applied to ESS and the AHI. MRI metrics are presented as a percentage of intracranial volume, except for covert brain infarcts. Bold values represent significant associations. Models were adjusted for age, age squared, sex, and time between ESS assessment, *APOE ε4* allele carriers, body mass index, sleeping pills, depression, and revised Framingham Stroke Risk Profile score, in addition to the presented additional covariates. AHI, Apnea-Hypopnea Index; CI, confidence intervals; ESS, Epworth Sleepiness Scale; MRI, magnetic resonance imaging; OR, odds ratio; SE, standard error; WRAT, Wide Range Achievement Test.

Secondary analysis: APOE ε4 allele carrier status, age and sex as moderators

APOE ε4 allele carrier status ($p = .008$) and sex ($p = .023$) moderated the relationship between continuous ESS scores and cortical gray matter volume. In *APOE ε4* allele carriers, higher ESS scores were associated with lower cortical gray matter volume at a trend level (β, *SE*: –0.364, 0.215; $p = .094$), while in non-carriers, higher ESS scores were significantly associated with higher cortical gray matter volume (β, *SE*: 0.428, 0.138; $p = .002$). Higher ESS scores were associated with higher cortical gray matter volume in men only (β, *SE*: 0.514, 0.164; $p = .002$), while no association was observed in women (β, *SE*: –0.011, 0.159; $p = .945$). No interaction with age or with other MRI metrics was observed.

Secondary analysis: global cognition and ESS scores

Higher ESS scores were associated with better global cognitive performance (β, *SE*: 0.176, 0.056; $p = .002$), which was still significant when further adjusting for the AHI (β, *SE*: 0.161, 0.058; $p = .006$). When looking at individual tests, the association between higher ESS scores and better cognitive performance was mostly driven by the Visual Reproductions Immediate and Delayed Recall (β, *SE*: 1.273, 0.408, $p = .002$) and the Hooper Visual Organization Test (β, *SE*: 0.105, 0.036, $p = .004$). Similarly, excessive daytime sleepiness (ESS > 10) was also associated with a better global cognitive performance (β, *SE*: 0.226, 0.091, $p = .013$), which was still significant when adjusting for the AHI (β, *SE*: 0.199, 0.095, $p = .036$).

Longitudinal analyses: changes in sleepiness, atrophy, and cognitive decline

Annualized increases in continuous ESS scores were associated with increasing volume of white matter hyperintensities (β, *SE*: 0.195, 0.086, $p = .024$). Annualized change in continuous ESS scores were not associated with baseline total brain volume (β, *SE*: 0.140, 0.180, $p = .437$), cortical gray matter volume (β, *SE*: 0.059, 0.153, $p = 0.699$), subcortical gray matter volume (β, *SE*: –0.011, 0.027, $p = .672$), covert brain infarcts (OD, CI: 0.905, 0.487–1.681, $p = .752$), or the composite cognitive score (β, *SE*: 0.018, 0.074, $p = .811$).

Between the four longitudinal sleepiness groups, stable non-sleepy individuals as compared to individuals with stable excessive daytime sleepiness had lower baseline total brain volume (adjusted means 77.49 (0.10) vs. 78.17 (0.26), $p = .015$). Individuals that developed excessive daytime sleepiness had lower baseline total brain volume (adjusted means 77.18 (0.35) vs. 78.17 (0.26), $p = .024$) and lower cortical gray matter volume (adjusted means 36.97 (0.30) vs. 38.22 (0.22), $p = .0008$) than those with stable excessive daytime sleepiness. Individuals with resolved excessive daytime sleepiness had lower baseline cortical gray matter volume than those with stable excessive daytime sleepiness (adjusted means 37.11 (0.29) vs. 38.22 (0.22), $p = .002$). No other differences were observed between these four groups.

No association between sleepiness levels and subsequent annualized atrophy (total brain volume, β, *SE*: –0.072, 0.076, $p = .345$; cortical gray matter volume, β, *SE*: –0.068, 0.080, $p = .399$) or cognitive decline (composite neuropsychological score, β, *SE*: 0.003, 0.007, $p = .643$) were observed.

Discussion

In cognitively healthy middle-aged and elderly participants from the community-based Framingham Heart Study, higher self-reported daytime sleepiness was associated with MRI markers that are indicative of a healthier brain, including larger total brain and cortical gray matter volume, fewer covert brain infarcts, and better cognitive performance. These associations were independent of several confounders, including cardiovascular diseases and risk factors, demographic variables, sleeping medications, and depression. Because our findings may seem counterintuitive, we performed a series of secondary analyses to better characterize our results. The associations between daytime sleepiness and MRI metrics were independent of obstructive sleep apnea severity, insomnia symptoms, habitual sleep duration, and nap frequency and duration. This suggests that the observed association was not accounted for by common sleep disturbances, sleep debt, or frequent daytime naps. Additionally, interactions revealed that the association of self-reported daytime sleepiness evidenced by higher ESS scores with larger cortical gray matter volume was only observed in men and noncarriers for the *APOE ε4* allele. Overall, our findings challenge the view that daytime sleepiness is a marker of brain

aging or ischemic damage when it is not a symptom of another pathology or sleep disorder.

Although some previous studies reported that daytime sleepiness was associated with global or regional atrophy [42–45], it was often in the presence of—or even accounted for by—sleep disturbances, including obstructive sleep apnea and shorter total sleep time. On the other hand, a few reports also observed larger gray matter volume in the context of sleepiness. Killgore et al. reported regional atrophy concomitant with other regions of larger volume over the frontal and occipital cortex in 36 participants in association with a higher ESS score [46]. Two groups reported that excessive daytime sleepiness in Parkinson's Disease was associated with larger striatum or hippocampus and parahippocampus [47, 48]. A larger precuneus has been found in relation to hypersomnia and associated daytime sleepiness [49], and daytime sleepiness following sleep deprivation has been associated with larger frontal gray matter regions [50]. In most of these studies, larger gray matter volumes in relation to sleepiness were hypothesized to represent structural plastic compensatory changes in the face of pathology or other functional changes to cerebral networks. To the best of our knowledge, this is the largest study in which enlarged gray matter has been linked with daytime sleepiness.

Larger gray matter volume is not always a sign of better integrity, since it has been reported in various pathological conditions [51–55], and could underlie a large array of pathological processes such as edema, inflammatory cell recruitment, astrogliosis, or amyloid deposition. However, it is unlikely that larger cortical gray matter volumes represent pathological processes in the present study, as we also observed that more daytime sleepiness was associated with less risk of presenting covert brain infarcts and better global cognitive performance. This suggests that larger total brain and cortical gray matter volumes also point to better brain integrity. Although it is not the case in all studies, better cognitive performance with more daytime sleepiness was reported previously as well [56, 57]. However, to the best of our knowledge, this is the first study to report that more daytime sleepiness is associated with a lower prevalence of covert brain infarcts.

The underlying cause of the association between more daytime sleepiness and markers of better brain integrity remains unclear. In fact, this finding is discrepant with many previous reports in which more daytime sleepiness was associated with higher dementia risk, cognitive decline, amyloid deposition, and stroke risk [14–17, 43, 58–60]. On the one hand, daytime sleepiness could arise as a symptom of sleep disturbances, health conditions, and underlying pathology, which would explain its association with elevated risk of dementia and stroke in those studies. On the other hand, daytime sleepiness could also reflect intact sleep–wake regulatory processes rather than a sleep debt. Our findings are consistent with this latter interpretation, especially since we included statistical adjustment for an array of risk factors, including markers of sleep disorders (obstructive sleep apnea, insomnia), and sleep debt (habitual sleep duration, naps). Sleepiness levels were neither associated with atrophy nor cognitive decline over time in our study. Moreover, those with stable excessive daytime sleepiness over time had higher total brain volume and cortical gray matter volume as compared to nonsleepy individuals or those with sleepiness that developed or resolved, suggesting a trait-like stable feature of individuals with persistent sleepiness. A large genome-wide association study reported that daytime sleepiness was related to polymorphisms of two sleep profiles: one that is associated with sleep propensity independent of sleep disturbances and another with sleep fragmentation [61], suggesting that sleepiness is complex and multifaceted. Daytime sleepiness was previously associated with sleep-preparatory behaviors and better sleep hygiene [62], and thus, some individuals with sleepiness may be more attuned to their body's signal and its presence may be a motivational sleep drive. Therefore, when it is not accounted for by sleep disturbances or health conditions, daytime sleepiness might be associated with markers of brain integrity via its role to promote sleep of a higher quality and/or quantity and adequate circadian timing. It is also possible that individuals with better brain integrity have a better assessment of their symptoms, and thus, report their sleepiness more accurately. For example, participants with Alzheimer's Disease sometimes have problems to accurately report their sleep disturbances [63, 64], suggesting that neurodegeneration impairs the ability to self-report sleep patterns. Overall, daytime sleepiness, when not accounted for by sleep disturbances or health conditions, may be a promoter or a marker of good brain integrity and intact sleep-regulatory processes.

Consistent with the hypothesis that daytime sleepiness is associated differently with brain integrity whether it is a symptom or not of an underlying disorder, we observed an interaction between *APOE* ε4 allele carrier status and daytime sleepiness in its association with cortical gray matter volume. More sleepiness was associated with larger cortical gray matter volume in non-carriers, while a trend in the opposite direction was observed in carriers. Daytime sleepiness might not be a marker of innate sleep propensity in carriers, who are at higher risk of developing Alzheimer's Disease, but rather a symptom of underlying pathology and neuronal dysfunction. We also observed that more daytime sleepiness was associated with larger cortical gray matter volume in men only. It is unclear why this association was observed in men only, but there are sex differences in how individuals report and experience sleepiness [65]. One previous study performed in men showed that excessive daytime sleepiness was associated with better sleep during a PSG recording [66], and thus, daytime sleepiness might be a more robust marker of innate sleep propensity in men.

An alternative hypothesis is that daytime sleepiness could also be the result of healthier daytime activities in middle-aged and elderly participants that promote cognitive reserve, leading to its association with markers of brain integrity. Older individuals generally tend to get less sleepy, which is hypothesized to be because of less functional expectations and higher schedule flexibility after retirement [67]. Although sleepiness is sometimes associated with a sedentary lifestyle, some studies have shown that spending more time at a computer or engaging in more physical activity correlates with higher levels of daytime sleepiness [40, 68]. Therefore, participants who engage in more cognitive and physically demanding activities might present with more daytime sleepiness and MRI metrics suggestive of less brain aging and ischemic damage. Although our results did not change when we adjusted for education or WRAT, these are only proxies for cognitive reserve or daytime mental load. We did not have additional information that could be used to infer cognitive reserve, such as occupational complexity. In our analyses, the continuous ESS scores were no longer significantly associated with MRI markers when adjusting for physical activity, suggesting that it may partly account for the association between daytime sleepiness and markers of better brain integrity. As physical activity has previously been associated with

greater gray matter volume [69] and a lower risk of dementia [70], some of our participants could have reported subclinical levels of sleepiness following higher levels of vigorous physical activity, although other individuals may be showing higher sleepiness as a cause or consequence of being less physically active [40, 71]. However, we found that the associations between ESS > 10 and total and cortical volumes remained significant when adjusting for physical activity, suggesting that physical activity may not fully account for the observed associations when excessive daytime sleepiness is present. Similarly, the associations between continuous ESS scores and MRI markers were no longer statistically significant after adjustment for coffee consumption. Coffee consumption might have affected how certain participants rated their sleepiness levels: caffeine is often consumed to reduce sleepiness, and thus, may be associated temporarily with lower levels of sleepiness [72]. On the other hand, people that are sleepy in the first place might consume more caffeine or experience more rebound sleepiness [72]. It remains unclear how caffeine plays a role in the association between sleepiness and brain health: The relationship between caffeine consumption and brain health is complex, with caffeine being associated with higher risk of intracranial hemorrhage [73], but with lower risk of brain ischemia [74] and greater gray matter volume in older adults [75]. As with physical activity, the potential confounding or mediating effect of coffee consumption in the association between sleepiness levels and brain volumes seem to be only present at the subclinical levels of sleepiness, since adjustment for coffee consumption did not diminish these associations with greater total brain and gray matter volumes when excessive daytime sleepiness (ESS > 10) was evaluated.

Strengths of this study included our large community-based sample and the rigorous adjustment for many potential confounders, including objectively measured sleep variables. Limitations of the study include the observational design, restricting our assessment of causality. A second limitation is that the measurement method used in the present study, the ESS, is a self-report measure. Sleepiness can be measured by several distinct objective and subjective measures, with poor correlation between methods. The poor inter-relationship between objective and subjective measures has been hypothesized to be caused by the different factors assessed by these tests. The ESS is the most commonly used questionnaire to assess self-reported sleepiness retrospectively [6, 22], and addresses sleep propensity, drowsiness, and sleep drive, while some objective measures seem to be addressing mostly the ability to fall asleep, alertness, and wake drive [22, 76]. Further studies should evaluate whether our findings extend to objective methods of evaluating sleepiness, such as the Multiple Sleep Latency Test. Additionally, our findings could be explored using other questionnaires assessing sleepiness, such as the Stanford Sleepiness Scale and the Karolinska Sleepiness Scale [6]. Whereas the Stanford Sleepiness Scale asks the participant to rate their current level of sleepiness using somewhat ambiguous terms (e.g. foggy, slowed down, and woozy), the Karolinska Sleepiness Scale assess current sleepiness levels at the time of the questionnaire with clearer terms (e.g. alert, sleepy, and fighting sleep) [6]. Another limitation is the ethnic composition of the Framingham Heart Study Offspring cohort, which mostly included Caucasian participants. As there are ethnic variations in self-reported sleepiness levels [77], this limits the generalizability of our findings.

Overall, our findings challenge the view that daytime sleepiness is always a negative sleep-wake dysfunction tied to poor health outcomes. In the present study, higher sleepiness was associated with MRI markers of better brain integrity. Thus, when it is not accounted for by sleep disorders or disturbances, or various health conditions, more daytime sleepiness may not necessarily be a sign of poorer brain integrity. Further studies should explore in which context sleepiness may be a promoter or a marker of positive innate sleep propensity versus when sleepiness represents sleep debt and diseases.

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