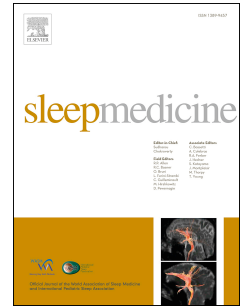


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Sleep and brain morphological changes in the eighth decade of life

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Subtitle: Sleep and brain changes in older people

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Abstract

Objective: Sleep is important for brain health. We analysed associations between usual sleep habits and MRI markers of neurodegeneration (brain atrophy), vascular damage (white matter hyperintensities, WMH) and waste clearance (perivascular spaces, PVS) in older community-dwelling adults.

Method: We collected self-reported usual sleep duration, quality and medical histories from the Lothian Birth Cohort 1936 (LBC1936) age 76 years and performed brain MRI. We calculated sleep efficiency, measured WMH and brain volumes, quantified PVS, and assessed associations between sleep measures and brain markers in multivariate models adjusted for demographic and medical history variables.

Results: In 457 subjects (53% males, mean age 76 ± 0.65 years), we found: brain and white matter loss with increased weekend daytime sleep ($\beta = -0.114$, $P = 0.03$; $\beta = -0.122$, $P = 0.007$ respectively), white matter loss with less efficient sleep ($\beta = 0.132$, $P = 0.011$) and PVS increased with interrupted sleep (OR 1.84 95% CI, $P = 0.025$).

Conclusion: Cross-sectional associations of sleep parameters with brain atrophy and more PVS suggest adverse relationships between usual sleep habits and brain health in older people that should be evaluated longitudinally.

Keywords: Sleep, perivascular spaces, brain atrophy, cerebrovascular disease, ageing, Magnetic resonance imaging

1.0 Introduction

Sleep is important for maintaining brain health. During sleep, the brain is thought to clear metabolic waste including proteins such as β -amyloid.(Shokri-Kojori, et al., 2018,Xie, et al., 2013) Impaired sleep may increase the risk of adverse cognitive and health outcomes,(Gadie, et al., 2017,Spiegelhalter, et al., 2015) and is associated with slower processing speed in older subjects.(Cox, et al., 2019) Furthermore, sleep disorders such as obstructive sleep apnoea (OSA) are associated with increased risk of cerebrovascular disease,(Seiler, et al., 2019,Sharma and Culebras, 2016) vascular lesions on magnetic resonance imaging (MRI) such as white matter hyperintensities (WMH),(Del Brutto, et al., 2017,Kim, et al., 2013,Song, et al., 2017) increased perivascular space (PVS) visibility,(Song, et al., 2017) and hippocampal atrophy.(Gadie, et al., 2017,Kim, et al., 2013,Owen, et al., 2018,Spiegelhalter, et al., 2015)

Less is known about whether usual sleep habits in community-dwelling older people are associated with neuroimaging changes. In cognitively normal, late middle-aged and older adults, short sleep duration was associated cross-sectionally with worse cortical and hippocampus atrophy,(Carvalho, et al., 2017,Sexton, et al., 2014,Spira, et al., 2016) and longitudinally, with more brain atrophy and cognitive decline.(Lo, et al., 2014,Sexton, et al., 2014,Sexton, et al., 2017) Poor sleep quality was associated with reduced white matter structural integrity on MRI in 448 community-dwelling subjects aged 60-82 years,(Sexton, et al., 2017) and with WMH (but not microbleeds or lacunes) in 311 older community-dwelling people.(Del Brutto, et al., 2015) However, in another community-based study (n=970), neither sleep quality nor duration were related to any small vessel disease (SVD) markers.(Zuurbier, et al., 2015) The different findings may reflect the wide range in ages and

background vascular risk, since all SVD lesions and brain atrophy worsen with advancing age and vascular risk factor exposure.

Despite interest in PVS and their role during sleep in rodents,(Iliff, et al., 2015) few studies have assessed usual sleep habits and PVS, or other vascular and neurodegenerative disease markers, in humans.(Song, et al., 2017) PVS are visible on T2- and T1-weighted brain MRI and are associated with other features of SVD, hypertension, cognitive impairment and dementia.(Debette, et al., 2018,Francis, et al., 2019,Passiak, et al., 2019) Two studies in patients with cerebrovascular disease and community-dwelling subjects (n=26 and n=97 respectively) found sleep abnormalities including sleep efficiency on polysomnography were associated with increased PVS visibility,(Berezuk, et al., 2015,Del Brutto, et al., 2019) and in a wider sample of 388 community-dwelling subjects including the 97 above, a univariate association between poor sleep quality and increased visible basal ganglia PVS was attenuated after co-variate adjustment.(Del Brutto, et al., 2019)

Based on self-reported sleep habits, we found previously that increased daytime sleep duration was associated with slower processing speed cross-sectionally, and with decline in visuospatial processing between ages 70 and 76 in community-dwelling subjects.(Cox, et al., 2019) In the current analysis, we assessed the same community-dwelling subjects at age 76 for associations between self-reported sleep habits and vascular (PVS, WMH) or neurodegenerative (whole or subregional brain volume loss) changes on MRI.

2.0 Methods

2.1 Subjects

Study participants were members of the Lothian Birth Cohort 1936 (LBC1936) who are community-dwelling older adults, all born in 1936, and living in South-East Scotland when recruited between 2004 and 2007.(Deary, et al., 2012) The LBC1936 underwent medical and cognitive assessments at mean ages 70 (n=1091, Wave 1), 73 (n=700, Wave 2), and 76 years (n=488, Wave 3),(Deary, et al., 2012,Deary, et al., 2007) brain MRI(Wardlaw, et al., 2011) at waves 2 and 3, and completed a short Sleep Questionnaire at wave 3. We used concurrent medical, MRI and sleep data from Wave 3 in the present analysis.

2.2 Regulatory

Written informed consent was obtained from all participants under protocols approved by the Lothian (REC 07/MRE00/58) and Scottish Multicentre (MREC/01/0/56) Research Ethics Committees. Participants provided demographic information and medical history including of cardiovascular disease, diabetes, hypertension, smoking (never, previously or current), hypercholesterolemia and stroke.(Deary, et al., 2007,Wardlaw, et al., 2014) We excluded participants with a diagnosis of dementia.

2.3 Sleep Variables

We used a short Sleep Questionnaire adapted from the Pittsburgh Sleep Quality Index.(Buysse, et al., 1989) As described previously,(Cox, et al., 2019) participants recorded their sleep *quality* in the last month (very bad=0, fairly bad=1, fairly good=2, very good =3). Based on Patient-Partner Questionnaire used in the Sleep Medicine Unit, Royal Infirmary Edinburgh (author RLR) participants also provided estimates of their typical *time spent in bed* and sleep *duration* for night-time and daytime on weekdays and weekends, sleep latency (time taken to fall asleep), and whether their night-time sleep was regularly *interrupted* (excluding awakenings for the toilet). We converted all sleep durations and time in bed to

hours for uniformity and calculated hours slept during the night (*night-time*), during the day (*daytime*), on *weekdays* and *weekends*. We calculated ‘*sleep efficiency*’ using the sleep timings as reported in the Patient-Partner questionnaire above and the principles described in (Berezuk, et al., 2015) as:

[Number of night-time hours slept ÷ total number of night-time hours spent in bed] x 100

2.4 Brain Magnetic Resonance Imaging and Feature Analysis

Whole brain MRI was performed on a 1.5T GE Signa Horizon HDx scanner (General Electric, Milwaukee, WI, USA) using a self-shielding gradient set with a maximum gradient strength of 33 mT/m, and an 8-channel phased-array head coil. The imaging data included: T₁-, T₂-, T₂*- and Fluid Attenuated Inversion Recovery (FLAIR)-weighted whole brain scans, all details described previously.(Wardlaw, et al., 2011).

All analyses were blind to sleep, medical, cognitive and all other parameters. We measured intracranial volume (ICV), total brain volume (TBV), WMH volumes, normal-appearing white matter (NAWM) and grey matter (GM) volumes, using a validated semi-automatic image analysis method.(Valdés Hernández, et al., 2015) We measured intracranial volume (ICV) using the Object Extraction Tool in the Analyze 9.0TM,(Wardlaw, et al., 2011) and expressed all brain and WMH volumes as the proportion of ICV (% ICV), indicating tissue loss from peak adulthood.(Royle, et al., 2013,Wardlaw, et al., 2011)

We assessed PVS in the basal ganglia (BG) and centrum semiovale (CS) on a validated four-point scale (where 0=none and 4=40 and above PVS per side),(Potter, et al., 2015) defined as previously.(Wardlaw, et al., 2013) The intra- and inter-rater kappa statistics for PVS rating were 0.89 in basal ganglia (BG), and 0.77 in centrum semiovale (CS).

2.5 Statistical analyses

We performed all statistical analyses using SPSS version 19 (IBM Inc. New York, USA), with all statistical tests being two-tailed, P values <0.05 considered statistically significant and a more rigorous value of $P<0.001$ to minimise spurious findings due to multiple comparisons. Sleep duration and measures of atrophy were normally distributed; sleep quality and interruption were categorical; sleep efficiency was left-skewed but could not be normalised by any standard transformation and therefore was not transformed. We log transformed WMH as it was very right-skewed. We compared gender, sleep efficiency and sleep duration using independent t-tests, and sleep quality and interruption using Mann-Whitney U test. We did not perform a power calculation since the sample was limited by the available cohort, but we were careful not to include too many co-variates, check the fit of models and set rigorous P values.

First, we examined consistencies amongst the sleep variables using bivariate analysis and Cronbach's alpha. Next, we examined associations between sleep variables and medical history (bivariate analysis) and lastly, we used multivariate linear regression models to examine associations between sleep variables and imaging parameters (PVS, % WMH in ICV and measures of atrophy) adjusted for medical and demographic variables. We ran models using each sleep variable as the dependent (outcome) variable and each brain volume, % WMH in ICV and PVS as the independent variable. Four models were developed in a step-wise manner, beginning with the dependent variable, independent variable, age and sex, then adding medical variables (diabetes, smoking, body mass index, cholesterol and blood pressure), then vascular disease (stroke, peripheral vascular disease and other circulatory

problems) and finally adding arthritis. Final covariates were sex, age in days at scanning, and self-reported history of cardiovascular disease, diabetes, hypertension, smoking, hypercholesterolemia and stroke. Similarly, we used regression to test the association between sleep efficiency and the predictor variables, correcting for all covariates. The residuals of the regression model were normally distributed, suggesting a good fit of the model. We assessed sleep quality and interruption (yes/no), PVS and atrophy using multinomial regression analysis with the sleep variable as the outcome and PVS, WMH and measures of atrophy as the predictor variables (reference category for quality outcome variable = 'very bad'), controlled for all covariates.

3.0 Results

3.1 Subjects: Of the 488 subjects who underwent brain MRI, 457 had complete sleep, brain MRI and clinical data, of whom 53% were male (Table 1). The mean age at MRI scanning was 76.31 ± 0.65 years (minimum 74.73, maximum 77.75 years). Almost half of the participants had hypertension, hypercholesterolemia or arthritis, were current or ex-smokers, 12% had diabetes, 33% had heart disease and 11% had previous stroke. The mean \pm SD WMH volume was 16 ± 15 ml, mean $1.1 \pm 1.0\%$ of the ICV. The median (IQR) basal ganglia PVS score was 1.0 (0) and centrum semiovale score was 2.0 (1.0). The TBV, NAWM, and GM occupied a mean \pm SD proportion of the ICV of $68 \pm 2\%$, $32 \pm 2\%$, and $32 \pm 2\%$ respectively. Males generally slept longer than females (Table 1).

3.2 Sleep measures, inter-relationships:

The sleep variables were internally consistent. Weekend and weekday sleep durations were highly correlated (eg at *nighttime* Pearson $r=0.970$, $P<0.001$, Supplementary Table S1, Cronbach's alpha 0.98). The following reflect weekday associations, with a similar pattern

seen for weekends (Supplementary Table S1): those who slept less during the night slept more during the day ($r=-0.20$, $P<0.001$) and had poorer sleep efficiency ($r=-0.11$, $P=0.007$). Night-time sleep duration correlated positively with sleep quality ($r=0.57$, $P<0.001$) and efficiency ($r=0.501$, $P<0.001$). Sleep efficiency correlated positively with sleep quality ($r=0.486$, $P<0.001$). Interrupted sleep was present in about 20% of the population and associated inversely with sleep efficiency ($r=-0.12$, $P=0.003$) and quality ($r=-0.25$, $P<0.001$).

3.3 Sleep, demographic and medical variables:

There were no associations between self-reported sleep variables and age, BMI, smoking habit or medical histories in adjusted models, apart from diabetes ($r=-0.10$, $P=0.012$) and arthritis ($r=-0.17$, $P<0.001$) both of which were associated with shorter night-time sleep (Supplementary Table S2).

3.4 Sleep and imaging variables:

Increased weekend daytime sleep duration was associated with reduced total brain and NAMW volumes ($\beta=-0.11$, $P=0.03$; and $\beta=-0.12$, $P=0.01$ respectively; Table 1, Figure 1). Lower sleep efficiency was associated with reduced NAWM volume ($\beta=0.13$, $P=0.011$, Table 2, Figure 2). There was no association between night-time sleep duration or sleep quality and brain volume losses, although the directions of effects were consistent.

Interrupted sleep was associated with more visible basal ganglia PVS (OR 1.84, 95% CI 1.08-3.15), but not WMH or brain volumes (Table 2).

Neither sleep duration, sleep quality or efficiency correlated with WMH (Table 2).

4.0 Discussion

We show that adverse usual sleeping habits, specifically increased day-time sleep and lower sleep efficiency, are associated with signs of neurodegeneration and cerebral microvascular dysfunction, when measured contemporaneously in a large sample of community-dwelling people aged around 76. Reduced white matter provides a mechanistic substrate for the association between increased daytime sleep and slower processing speed found previously in this cohort.(Cox, et al., 2019) The association between interrupted sleep and increased PVS visibility suggests that sleep disturbance might affect brain waste clearance, or vice versa. The lack of association in this study between usual sleep habits and WMH may be due to the co-association between age and WMH reflected in wider age-ranges in prior studies. This is, to the best of our knowledge, the largest and only study to assess contemporaneous associations between sleep duration, quality, efficiency, interruption and MRI markers of cerebrovascular and neurodegenerative disease at older ages. These cross-sectional associations require testing in longitudinal studies to determine whether alterations in usual sleep habits lead to development of vascular and neurodegenerative lesions, or vice versa, in older age.(Gadie, et al., 2017,Scullin, 2017)

Brain atrophy is associated with cognitive decline, dementia and early death (Cole, et al., 2018) and impaired sleep may increase the risk of adverse cognitive and health outcomes.(Gadie, et al., 2017,Spiegelhalder, et al., 2015) The independent association of reduced white matter (and total brain) volume with adverse sleep parameters of increased weekend daytime sleep and poorer sleep efficiency is novel since previous studies reported on cortical or hippocampal volume loss but not white matter loss.(Carvalho, et al., 2017,Lo, et al., 2014,Sexton, et al., 2014,Spira, et al., 2016) Reasons for the absence of association of brain volume loss with night-time or weekday daytime sleep in our study are unclear although the direction of effect was consistent. The subjects were all past conventional UK

retirement age but nonetheless may have had weekday commitments and more time to rest during the day at weekends. The finding is consistent with the Honolulu-Asian Ageing Study (n=167) which found that reduced slow wave sleep identified with polysomnography was associated with brain atrophy at post-mortem on average 10 years later.(Gelber, et al., 2015)

The association of increased PVS with interrupted sleep is also notable. PVS are pathways for clearing interstitial fluid and metabolic waste which is thought to increase during sleep, at least in rodents.(Iliff, et al., 2015) Increased PVS on MRI associate with SVD, hypertension, cognitive decline and dementia.(Debette, et al., 2018,Francis, et al., 2019,Passiak, et al., 2019) Increased PVS visibility was associated cross-sectionally with abnormal sleep efficiency in two studies on polysomnography,(Berezuk, et al., 2015,Del Brutto, et al., 2019) but an association with sleep quality did not survive co-variate adjustment in a larger sample of community-dwelling subjects.(Del Brutto, et al., 2019) Sleep efficiency reflects some elements of interrupted sleep that we found to be associated with increased basal ganglia PVS in co-variate-adjusted analysis in the present study. These findings require confirmation in larger studies in other populations and in longitudinal analysis. Data on PVS *function* in humans, including in wakefulness versus sleep, is very limited.(Ringstad, et al., 2017) If sleep is important for PVS fluid clearance in humans, then enlargement of the PVS in subjects with interrupted sleep might indicate fluid stagnation and waste deposition in PVS, consistent with increased β -amyloid seen in brain and CSF with short-term sleep disruption in volunteers.(Ju, et al., 2017,Shokri-Kojori, et al., 2018,Varga, et al., 2016) However, the present cross-sectional study does not determine the direction of association and it is possible that sleep interruption might reflect adverse effects of dilated PVS on sleep control centres in the hypothalamus. These findings will be examined in longitudinal studies to determine the direction of effect.

We did not find associations between WMH, a common marker of vascular disease and dementia,(DeBette, et al., 2018,Georgakis, et al., 2019) and sleep variables, but the study may have been underpowered to detect a small association. However, with 457 subjects, this is the largest study of usual sleep habits and brain changes to date. Our findings concur with one other community-based sample with a wide age range(Zuurbier, et al., 2015) but not with several other studies which included populations with more vascular disease or pathological sleep, e.g. 237 persons of poor cardiovascular health mean age 70 where poor sleep quality was associated with WMH,(Del Brutto, et al., 2015) 170 subjects with clinically-defined OSA in whom the severity of sleep apnoea was independently associated with WMH(Song, et al., 2017) and 104 persons in whom OSA was associated with WMH.(Del Brutto, et al., 2017,Ramirez, et al., 2015,Sharma and Culebras, 2016) The absence of an association between sleep measures and WMH in the LBC1936 may reflect that WMH may be associated with OSA specifically (rather than usual sleep habits), that LBC1936 subjects have better average cardiovascular health than populations attending sleep clinics, the wider age range of subjects in other studies increasing the risk of confounding WMH associations by age, or the lower sensitivity of self-reported sleep variables versus polysomnography. However, the sleep questionnaire detected small differences in sleep variables between men and women, in those with diabetes or arthritis in the current analysis, and with subtle changes in cognitive function in prior analysis,(Cox, et al., 2019) suggesting that it is sensitive to modest associations with other variables. We suggest that further analyses of associations between sleep variables and WMH are required in populations with high or low cardiovascular risk profiles and/or pathological sleep complaints to determine if the association of sleep parameters and WMH is skewed by patient characteristics or increases in pathological sleep states.

The study strengths include the large sample, narrow age range minimising the confounding effect of age, and use of extensively validated imaging measurements. The study limitations included use of a self-report questionnaire rather than polysomnography or other recording device. This may have reduced our sensitivity for detecting modest associations between sleep timings, including the derived variables such as sleep efficiency, and brain changes. However, devices may not be completely reliable, our sleep measures were internally consistent and identified small but significant differences for some characteristics including cognition. (Cox, et al., 2019) Longer night-time sleep duration, better sleep quality and sleep efficiency were all positively correlated; reduced night-time sleep was associated with more daytime sleep, interrupted sleep and lower sleep quality. These consistent associations support the reliability and validity of self-reported sleep data. (Buysse, et al., 1989, Cox, et al., 2019) The association of diabetes and arthritis with shorter night-time sleep duration is unsurprising since diabetes may increase nocturia and arthritis causes discomfort. As noted above, the study may have been underpowered to detect some subtle associations, although to the best of our knowledge it is the largest study to date to assess sleep variables and age-associated brain lesions. We did not perform a power calculation since the sample was limited by the available cohort. Computational methods to assess PVS are now emerging (Ballerini, et al., 2018) which can quantify not only PVS count and total volume but also individual PVS length, width, size, sphericity, location and orientation and these may prove to be far more sensitive in future analysis to subtle associations between early PVS pathology and sleep habits. We did not assess, or control for, the influence that respiratory function, body mass index, use of medications, mood or presence/absence of a partner might have on sleep since the current focus was brain vascular and neurodegenerative markers and

sleep, corrected for common vascular risk factors and diseases that are known to affect SVD features.(Debette, et al., 2018,Georgakis, et al., 2019)

Sleep is important for brain health. One night of sleep deprivation,(Shokri-Kojori, et al., 2018) deliberately interrupted slow-wave sleep,(Ju, et al., 2017) and reduced slow-wave sleep(Varga, et al., 2016) are associated with increased B-amyloid in the brain(Shokri-Kojori, et al., 2018) or CSF(Ju, et al., 2017,Varga, et al., 2016) of healthy volunteers. The association of reduced sleep duration, quality, efficiency and increased sleep interruption with brain atrophy and increased PVS provides structural correlates whereby sleep impairment might affect brain health. Future research should address long-term associations of sleep parameters with neuroimaging markers of neurodegeneration and vascular disease, and with cross-sectional or longitudinal measures of cognitive and physical function and general health.

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Author Contributions

BSA, data collection, statistical and image analysis, drafting of paper

RLR, sleep questionnaire design, critical comment, editing of paper

MVH, data collection, image analysis, critical comment, editing of paper

SMM, data collection, image analysis, critical comment, editing of paper

SC, data collection including subject assessment, editing of paper

RR, data collection including subject assessment, editing of paper

AT, recruitment, subject assessment, editing of paper

AP, recruitment, subject assessment, editing of paper

JC, recruitment, subject assessment, editing of paper

PR, data management, editing of paper

MEB, data collection, study design, editing of paper

JS, study design, data collection, editing of paper

ID, study design, data collection, analysis, critical comment, editing of paper

JMW, study design, data collection, analysis, drafting and editing of paper and approval for final submission.

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Figure Legends:

Figure 1: Scatter plot with regression line showing associations between (a) Daytime sleep duration at weekends and % TBV in ICV and (b) Daytime sleep duration at weekends and % NAWM in ICV. Note, Beta (p values) account for all covariates in the models, including age, sex, diabetes, smoking, BMI, cholesterol, high blood pressure, stroke, cardiovascular disease, peripheral vascular disease and arthritis. TBV = Total Brain Volume. ICV = Intracranial Volume. NAWM = Normal Appearing White Matter.

Figure 2: Scatter plot with regression line showing associations between (a) Sleep efficiency and % NAWM in ICV and (b) Sleep efficiency and % WMH in ICV. Note, Beta (p values) account for all covariates in the models, including age, sex, diabetes, smoking, BMI, cholesterol, high blood pressure, stroke, cardiovascular disease, peripheral vascular disease and arthritis. TBV = Total Brain Volume. ICV = Intracranial Volume. NAWM = Normal Appearing White Matter.

Table 1: Demographic, health, sleep and imaging parameters for the study population

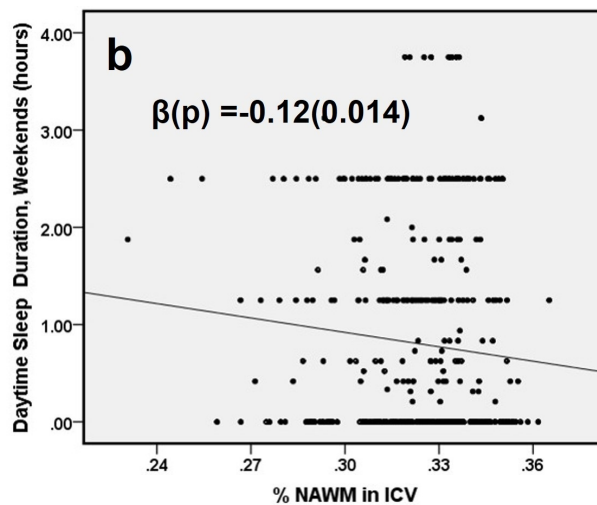
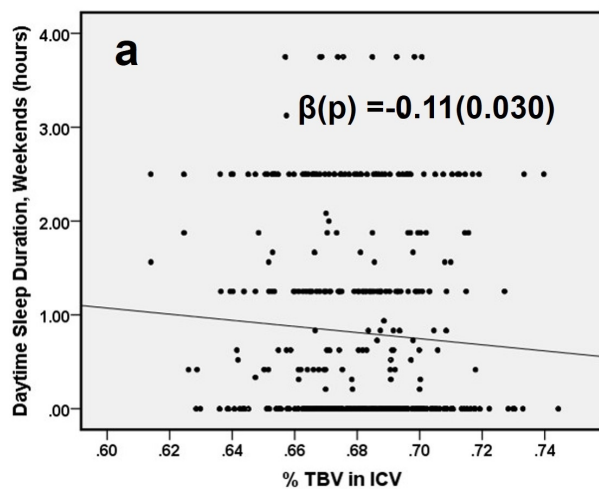
N=457	Measures	Mean (SD)		
Demographic	Age in years, mean (SD)	76.31(0.65)		
	% men	53		
		YES	NO	
Health conditions	Hypertension (%)	55	45	
	Diabetes (%)	12	88	
	Prior stroke (%)	11	89	
	Smoking (%) current or ever smoked	49	51	
	Hypercholesterolemia (%)	47	53	
	Cardiovascular (Heart) disease (%)	33	67	
	Peripheral vascular disease (%)	21	79	
	Arthritis (%)	47	53	
Sleep Variables	Measures of sleep		Mean (SD)	
	Night-time sleep duration (hours)	Weekdays	M: 6.92 (1.25), F: 6.73 (1.34)	
		Weekends	M: 7.00 (1.29), F: 6.79(1.36)*	
	Day-time Sleep duration (hours)	Weekdays	M: 1.21 (1.61), F: 0.85(1.2)**	
		Weekends	M: 1.19 (1.68), F: 0.79(1.19)**	
	Sleep efficiency weekdays (%)		M: 94.27(5.88), F: 91.73(7.85) **	
	Sleep efficiency weekends (%)		M: 95.49(5.60), F: 91.65(8.31) **	
	Sleep Quality, Median and IQR,		2 (1), of 4 categories	
	Interrupted sleep		NO = 82%	YES = 18%
Brain Imaging findings	PVS BG, Median (IQR)		1 (0)	
	PVS CS, Median (IQR)		2 (1.00)	
		Mean (SD)	% in ICV, Mean (SD)	
	ICV (ml)		1439.04(1367)	
	TBV (ml)		975.73(90.69)	68 (21)
	WMH (ml)		15.86(14.64)	11 (10)
	NAWM (ml)		464.59(53.21)	32 (20)
	GM (ml)		465.79(43.31)	32 (20)

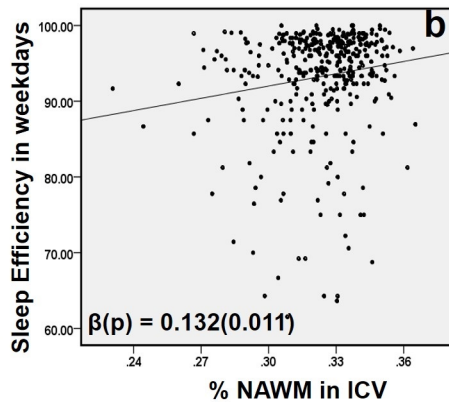
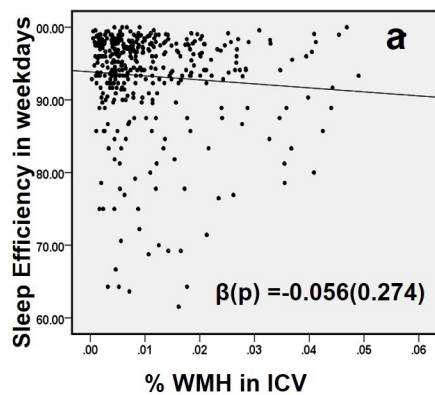
Note. BG = Basal Ganglia, CS = Centrum Semiovale, PVS = Perivascular Spaces, WMH = White Matter Hyperintensity, NAWM = Normal Appearing White Matter. GM = Grey Matter. TBV = Total Brain Volume. ICV = Intracranial Volume, CVD = cardiovascular disease, M= Male, F=Female, * Male significantly different from female at $P<0.01$. ** Male significantly different from female at $P<0.001$, Independent t-test. ** Male significantly different from female at $P<0.001$, Mann-Whitney U test.

Table 2: Linear regression models (A, C) and multinomial regression models (B), all fully adjusted, for the association between sleep duration, interrupted sleep, sleep efficiency and brain parameters.

A	Night-time sleep duration, weekdays,	Night-time sleep duration, weekends	Day-time sleep duration, weekdays	Day-time sleep duration, weekends
	Standardized β (P value)			
PVS BG	0.078 (0.092)	0.077 (0.099)	-0.035(0.461)	-0.031(0.517)
% WMH	0.000 (0.980)	0.000 (0.970)	0.05 (0.28)	0.06 (0.25)
% TBV	-0.038 (0.453)	-0.051 (0.321)	-0.075(0.151)	-0.11(0.030)
% NAWM	-0.031 (0.524)	-0.036 (0.465)	-0.09(0.07)	-0.12(0.014)
B	Interrupted Sleep			
	OR (95% CI)	SE	P value	
PVS BG	1.84 (1.08,3.15)	0.273	0.025	
% WMH	6.13 (0.00,999.99)	13.153	0.89	
%TBV	99.9 (0.04,99.99)	6.722	0.139	
%NAWM	0.69 (0.00,999.99)	6.736	0.956	
C	Sleep Efficiency			
	Standardized β (P value)			
PVS BG	-0.029 (0.562)			
% WMH	-0.056 (0.274)			
%TBV	0.067 (0.217)			
%NAWM	0.13 (0.011)			

Note. Sleep variables were the dependent variables while brain parameters were the independent variables. Distinct models were run for each sleep variable and brain parameter. These final fully adjusted models accounted for age, sex, diabetes, smoking, BMI, Cholesterol, high blood pressure, stroke, cardiovascular disease, peripheral vascular disease, other circulatory problems and arthritis. PVS BG = Perivascular spaces in the Basal Ganglia; WMH = White matter hyperintensities; TBV=total brain volume; NAWM=normal appearing white matter.





Highlights

- Adverse usual sleep habits associate with key brain changes in older people.
- White matter loss may explain association of daytime sleep and processing speed.
- PVS increase with interrupted sleep may indicate impaired brain waste clearance.
- These findings may explain why usual sleep is important for older brain health.