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Sleep quality, perivascular spaces and brain health markers in ageing - A longitudinal study in the Lothian Birth Cohort 1936

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ABSTRACT

Background: Sleep is thought to play a major role in brain health and general wellbeing. However, few longitudinal studies have explored the relationship between sleep habits and imaging markers of brain health, particularly markers of brain waste clearance such as perivascular spaces (PVS), of neurodegeneration such as brain atrophy, and of vascular disease, such as white matter hyperintensities (WMH). We explore these associations using data collected over 6 years from a birth cohort of older community-dwelling adults in their 70s.

Method: We analysed brain MRI data from ages 73, 76 and 79 years, and self-reported sleep duration, sleep quality and vascular risk factors from community-dwelling participants in the Lothian Birth Cohort 1936 (LBC1936) study. We calculated sleep efficiency (at age 76), quantified PVS burden (at age 73), and WMH and brain volumes (age 73 to 79), calculated the white matter damage metric, and used structural equation modelling (SEM) to explore associations and potential causative pathways between indicators related to brain waste cleaning (i.e., sleep and PVS burden), brain and WMH volume changes during the 8th decade of life.

Results: Lower sleep efficiency was associated with a reduction in normal-appearing white matter (NAWM) volume ($\beta = 0.204$, $P = 0.009$) from ages 73 to 79, but not concurrent volume (i.e. age 76). Increased daytime sleep correlated with less night-time sleep ($r = -0.20$, $P < 0.001$), and with increasing white matter damage metric ($\beta = -0.122$, $P = 0.018$) and faster WMH growth ($\beta = 0.116$, $P = 0.026$). Shorter night-time sleep duration was associated with steeper 6-year reduction of NAWM volumes ($\beta = 0.160$, $P = 0.011$). High burden of PVS at age 73 (volume, count, and visual scores), was associated with faster deterioration in white matter: reduction of NAWM volume ($\beta = -0.16$, $P = 0.012$) and increasing white matter damage metric ($\beta = 0.37$, $P < 0.001$) between ages 73 and 79. On SEM, centrum semiovale PVS burden mediated 5% of the associations between sleep parameters and brain changes.

Conclusion: Sleep impairments, and higher PVS burden, a marker of impaired waste clearance, were associated with faster loss of healthy white matter and increasing WMH in the 8th decade of life. A small percentage of the effect of sleep in white matter health was mediated by the burden of PVS consistent with the proposed role for sleep in brain waste clearance.

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1. Introduction

Sleep is important for maintaining brain health. During sleep, the brain is thought to clear metabolic waste, proteins, and cell debris that accumulate during daytime brain activity [1,2], maintaining the brain's physiological health through interconnected systems of neuronal activity and interstitial and cerebrospinal fluid (CSF) flow [1,3]. Pre-clinical studies have shown that during sleep, CSF filtration along the perivascular spaces (PVS) increases, thus increasing interstitial solute clearance [2]. When enlarged, PVS are visible on brain magnetic resonance imaging (MRI). Although the impact of an increased number of MRI-visible PVS in terms of overall health is still unknown, PVS volume and number increase with increasing age [3,4], are associated with vascular risk factors such as hypertension [7], markers of small vessel disease such as WMH and adverse health outcomes [8]. Cross-sectional clinical studies have reported an increase in PVS visibility is associated with markers of sleep impairment [5–7].

Sleep impairments tend to increase with age [8], and may be associated with increased risk of adverse health outcomes like stroke and ischaemic heart disease [9]. Sleep quality markers have been associated with several structural indicators of deteriorating brain health, namely white matter hyperintensities (WMH) of presumed vascular origin, microbleeds [10], and loss of normal appearing brain tissue [7,11,12], all assessed using MRI. However, studies demonstrating definitive causal associations of sleep and brain tissue health over time in community-dwelling older adults are lacking.

Here, we analyze longitudinal data from community-dwelling older adults of the Lothian Birth Cohort 1936 (LBC1936; Lothian Birth Cohorts | The University of Edinburgh): a large population-based study of cognitive, brain and general ageing, to identify any association between self-reported sleep duration, quality, and efficiency, PVS burden at the beginning of the 8th decade of life, and deterioration in normal and abnormal brain volumes across the decade, using structural MRI. Where associations exist, we investigated whether or not the PVS burden influences the association between sleep and brain structural changes over a period of time. We tested three hypotheses, (1) Sleep measures are associated independently with later deterioration in brain tissue, (2) PVS burden is associated with deterioration in brain tissue and (3) the association between sleep and structural brain changes is partly mediated by the PVS burden.

2. Methods

2.1. Subjects

Study participants were community-dwelling older adults, all born in 1936 in Edinburgh and The Lothians, from the LBC1936 Study [10–16]. The study was designed as a follow-up to the Scottish Mental Survey 1947, filled by all 11-years old Scottish children in full education at the time. As part of the LBC1836 Study, participants underwent detailed medical and cognitive assessments at mean age 70 years (Wave 1). Afterwards, every three years (Waves 2–4), study participants undertook the same medical and cognitive examinations and, additionally, had brain MRI starting at Wave 2 at mean age 73 years. In the Wave 3 examinations, at mean age 76 years, study participants also completed a short Sleep Questionnaire. From the 1062 Wave 1 study participants invited for Wave 2, 866 enrolled and 700 provided brain MRI data. For Wave 3, 820 were invited (18 withdrawn and 28 deaths), 697 enrolled and 488 completed the MRI scan. For Wave 4, 683 were invited (10 withdrawn and 34 deaths), 550 enrolled and 388 provided MRI data. Caring responsibilities, health issues, residential change,

intolerance for MRI/long examinations, and ineligibility for the study due to illness were among the main causes for dropout at each wave. The current analysis used MRI data from Waves 2, 3, and 4, and sleep data from Wave 3. A diagram of the recruitment across waves is provided in the supplementary materials.

Ethical permission for the Lothian Birth Cohort 1936 (LBC1936) study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland (Wave 1: MREC/01/0/56), the Lothian Research Ethics Committee (Wave 1: LREC/2003/2/29), and the Scotland A Research Ethics Committee (Waves 2 to 4: 07/MRE00/58). Enrolled participants at each wave provided demographic information and self-reported history of cardiovascular disease, diabetes, hypertension, smoking (never, previously or current), hypercholesterolemia and stroke, as it has been described previously [15].

2.2. Sleep variables

At age 76 (Wave 3), the study used a short Sleep Questionnaire adapted from the Pittsburgh Sleep Quality Index questionnaire [17] to collect information from participants about their sleep *quality* in the previous month (very bad = 0, fairly bad = 1, fairly good = 2, very good = 3). Study participants filled the questionnaire, which was posted to them. We also collected information on eight sleep variables: 1) usual time going to bed on weekdays, 2) usual time going to bed at weekends, 3) usual time staying in bed before sleeping on weekdays, 4) usual time staying in bed before sleeping at weekends, 5) usual time to wake up on weekdays, 6) usual time to wake up at weekends, 7) sleep quality and 8) sleep interruption (see variables' list in <https://www.ed.ac.uk/lothian-birth-cohorts/data-access-collaboration>). As described previously [18,19] these variables were used to calculate sleep duration at nights during the week and sleep duration at nights during the weekends (equation (1)), sleep duration during daytime on weekdays and sleep duration during daytime at weekends. We converted all sleep durations to hours, and calculated sleep *efficiency* at weekends and weekdays (equation (2)) [20,21].

$$\text{Sleep duration} = (\text{wake time} + 24 - \text{sleep time}) * 60 - \text{time staying in bed before sleep} \quad (1)$$

where:

Wake time = wake up time, clock time in hours

Time staying in bed before sleep = time in bed before sleeping, measured in minutes.

$$\text{Sleep Efficiency} = \left[\frac{\text{Number of night-time hours slept}}{\text{number of night-time hours spent in bed}} \right] * 100\% \quad (2)$$

2.3. Brain magnetic resonance imaging

At each wave (from Wave 2 onwards), whole brain MRI was performed on the same scanner, model Signa Horizon HDx (General Electric, Milwaukee, WI, USA), at 1.5T, using a self-shielding gradient set with a maximum gradient strength of 33 mT/m, and an 8-channel phased-array head coil. The structural image acquisition protocol included: T₁-, T₂-, T₂*- weighted and Fluid Attenuated Inversion Recovery (FLAIR)-weighted whole brain scans, with sequence details described in detail previously [11].

WMH in Wave 2 were segmented using multi-level threshold-based in-house semi-automated software that combines FLAIR

with the T2-star MRI sequences and quantifies the multispectral image space using minimum variance quantisation to allow better tissue discrimination [22]. For subsequent waves, this approach was automated using only the FLAIR-normalised intensities [23]. A Bland-Altman analysis comparing the two approaches ($n = 642$) showed a mean difference in WMH of only 0.049 ml ($SD = 471$). All raw segmentation results were also visually checked and manually edited for accuracy in all waves, where necessary. Intracranial volume (ICV) was extracted and measured using the Object Extraction Tool in Analyze 9.0™ as previously described [24]. The total brain tissue volume is the actual brain tissue excluding the ventricular CSF, CSF refers to all CSF inside the cranial cavity including the ventricles and superficial subarachnoid space, the grey matter comprises all grey matter in cortex and subcortical regions, and normal-appearing white matter refers to NAWM, areas of white matter not affected by WMH. The brain tissues were extracted and quantified using FAST [23], from the FMRIB Software Library (FSL), from T1-weighted images after ICV extraction. The output from FSL-FAST was automatically rectified using the WMH binary masks. Old infarcts were semi-automatically delineated as previously described [25] and removed from all masks. The proportion of each of the normal tissues, CSF and WMH volumes in ICV (% ICV) was computed and used in the statistical analyses to normalise all volume measures to compensate for inter-subject differences in head sizes [26]. We also assessed an additional measure of white matter damage, called the 'white matter damage metric' (WMD metric) that accounts for volume *and* severity of WMH with respect to the remaining NAWM. It is calculated as the proportion of WMH in the brain tissue excluding the cortex, weighted by the relative image contrast of the WMH with respect to the normal-appearing tissue in the FLAIR sequence, normally used to detect WMH [27].

We identified PVS in T2-weighted images as punctate or linear CSF-isointense lesions, hyperintense with respect to brain parenchyma, located in the course of penetrating arterioles/venules, less than three mm in diameter [11]. We quantified PVS in Wave 2 MRI (i.e. at age 73) in two ways. First, by visual scoring, a neuro-radiologist, blind to all other information, rated PVS in the basal ganglia and centrum semiovale on a validated four-point scale (0 = none, 1 = 1 to 10, 2 = 11 to 20, 3 = 21 to 40 and 4 = 40 and above PVS per side) [28]. Left and right sides were rated separately, then summed for a 'total' score. Another Neuro-radiologist cross-checked 20% of the scans giving intra- and inter-rater kappa statistics for basal ganglia (BG) PVS of 0.87 and 0.90, and centrum semiovale (CS) PVS of 0.75 and 0.80 respectively. Second, we used computational methods to assess PVS volume and count, blind to neuroradiological ratings, in the supraventricular centrum semiovale (CSO) white matter using a validated method [29]. The computational measures were visually checked, and cases where these measurements were deemed inaccurate e.g., due to movement artefacts were discarded.

2.4. Statistical analyses

Except where stated below, all statistical analyses were performed using the R programming language version 2.4. All statistical tests were two-tailed with a nominal alpha <0.05. Sleep duration and measures of atrophy (except WMH) 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 duration using independent t-tests, sleep efficiency using Man-Whitney U test, and sleep quality and interruption using Chi-Square test. We corrected all brain volumetric measurements

by ICV by using in the models the percentage of their volume in ICV. The PVS volume was adjusted by the overall brain tissue volume (TBV) where indicated, and is referred to as %PVS in TBV.

Consistencies amongst the sleep variables measured at age 76 were examined using bivariate analysis and Cronbach's alpha. Associations between PVS at age 73, sleep at age 76 and brain volumes from ages 73 to 79 were assessed using structural equation modelling (SEM) using Mplus version 8.6 [30]. Sleep and PVS were the predictor variables while the outcome variables were brain volumes, both the level and change in each outcome variable were computed using SEM. Specifically, we estimated the levels and changes in the longitudinal brain imaging parameters using latent growth curve (LGC) modelling. Models were implemented using full information maximum-likelihood to use all available data to minimise the potential bias that can be introduced by looking at generally more healthy completers [31]. First, we fitted a separate LGC SEM for each brain MRI variable – sleep measure pairing; in each case the level and change were the outcome variable, where each sleep variable measured at age 76 was the predictor. In Model 1, we corrected for sex and within-wave variance in age at each assessment (a time-varying covariate that was scaled to mean = 0, std. dev. = 1). In Model 2, we additionally corrected for self-reported diabetes, smoking, stroke, cardiovascular disease, hypertension and hypercholesterolaemia, alongside BMI, as measured at the initial assessment.

Next, we assessed the associations between computational and visual assessments of PVS at baseline (age 73 years) and subsequent brain structural changes (73–79 years). We fitted these models in the SEM framework above with the intercepts and slopes of each brain structural measure as outcomes and computational (computed/counted, PVS volume, %PVS in TBV) and visually-assessed (PVS rated in basal ganglia and centrum semiovale) PVS measures as predictors. Two separate models were fitted for each PVS-brain structural pair. The first was corrected only for sex (and age, as outlined above to correct for within-wave age variance). The second additionally corrected for vascular risk factors to investigate how much of the PVS-subsequent brain change effect is, in fact, due to vascular risk factors: self-reported diabetes, smoking, stroke, cardiovascular disease, hypertension and hypercholesterolaemia, alongside BMI.

Finally, to assess the degree to which having initially greater PVS load was a precursor to sleep-related brain structural changes (particularly with respect to subsequent white matter changes), we included % PVS in TBV as an additional covariate to Model 2. We refer to this as Model 3. The outcome of interest was the degree to which sleep associations with brain changes were attenuated with the inclusion of PVS.

Fully standardised coefficients were reported for all SEMs. We report model fit according to the Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI), the Root Mean Square Error of Approximation (RMSEA), and the Standardised Root Mean Square Residual (SRMR). We note that the residual of white matter damage at age 79 was fixed at zero in Models 2 and 3 to allow the models to converge on within-bounds estimates. It is important to note that we focus here on the longitudinal associations among variables; LGCM necessarily estimate both intercepts and slopes, and whereas we report the intercept associations for completeness, we note that cross-sectional sleep-brain associations in these data have been reported previously [5]. In that study, we found association between brain tissue loss (particularly in the white matter tissue) and reduced sleep, suggesting an adverse effect of poor sleep habit on brain health.

3. Results

3.1. Sample characteristics

We included data from 388 LBC1936 Study participants who

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

Category	Measures	Wave 2 (n = 700)	Wave 3 (n = 488)	Wave 4 (n = 388)
Demographic	Age, mean (SD)	72.53 (0.70)	76.30 (0.67)	79.37(0.60)
	% men	52	53	52
	Body Mass Index, mean (SD)	27.739 (4.329)		
Clinical	Hypertension (%)	49	55	
	Diabetes (%)	9	12	
	Prior stroke (%)	6	10	
	Current or recent smoker (vs. never) (%)	49	48	
	Hypercholesterolaemia (%)	42	48	
	Arthritis (%)	47	48	
	Peripheral vascular disease (%)	17	21	
	Cardiovascular disease (%)	27	32	
Sleep Variables	Measures of sleep		Mean (SD)	
	Night-time sleep duration, Weekdays (hours)		M: 6.92 (1.25), F: 6.73 (1.34)	
	Night-time sleep duration, Weekends (hours)		M: 7.00 (1.29), F: 6.79(1.36)*	
	Day-time sleep duration, Weekdays (hours)		M: 1.21 (1.61), F: 0.85(1.2)**	
	Day-time sleep duration, Weekends (hours)		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, 4 categories		2(1)	
	Interrupted sleep (%)		18	
	Imaging - PVS	PVS BG, median [QR1 QR3]	1 [12]	1 [11]
PVS CS, median [QR1 QR3]		2 [23]	2 [12]	
Imaging – Brain Tissue	NAWM volume (ml), Mean (SD)	478.10 (50.22)	465.27 (53.33)	456.84 (54.91)+
	GM volume(ml), Mean (SD)	474.97 (44.90)	466.38 (43.56)	464.93 (44.97)+
	TBV (ml), Mean (SD)	993.54 (89.75)	976.91 (90.81)	965.83 (89.54)+
	WMH (ml), Median [QR1 QR3]	7.82 [4.10 15.10]	11.01 [5.69 21.53]	14.12 [7.24 26.55]+
	White Matter Damage metric (median [QR1 QR3])	0.0057 [0.0026 0.012]	0.0087 [0.0041 0.019]	0.012 [0.006 0.024]

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. 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. + % of brain tissue volume in ICV significantly different between wave 2, 3 and 4 using independent t -test at $P < 0.001$.

provided answers to the Sleep Questionnaire at Wave 3 (age ~76 years). Table 1 shows the demographics, clinical, and imaging characteristics of the sample, as well as the sleep quality and efficiency parameters. The latter, split by biological sex, are given in a previous publication [5]. A graphical representation of the brain

tissue (i.e., normal and abnormal) changes across waves can be seen in Fig. 1. PVS in the centrum semiovale and corona radiata supra-ventricular, calculated in Wave 2, occupied 3.21 (SD 1.42) ml (i.e., less than 0.3% of ICV). Details, including width, length and size of individual PVS in the sample, have been previously published [29].

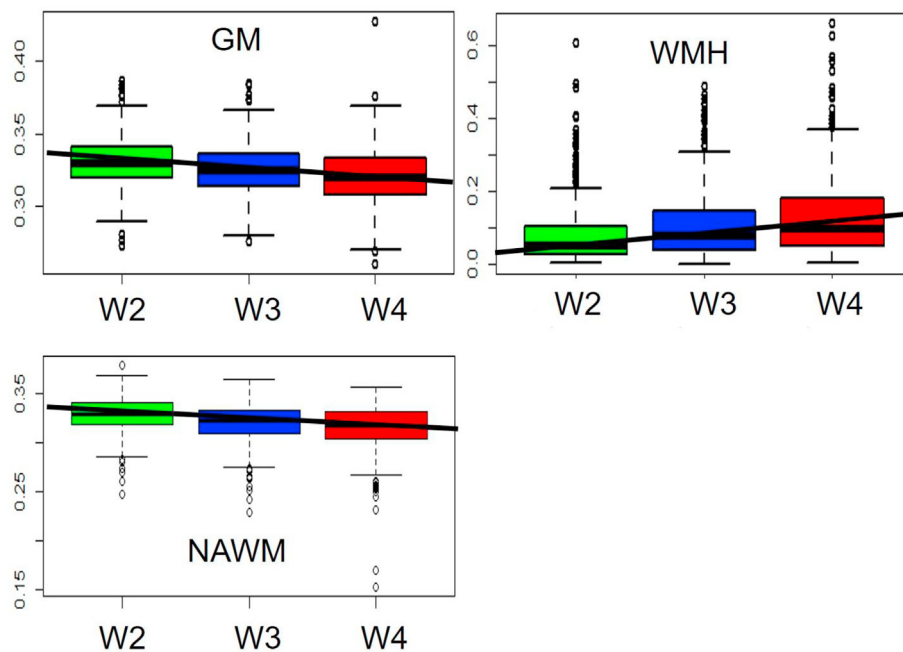


Fig. 1. Top left – The % of grey matter (GM) in ICV for the 3 waves (W), W2 (Green), W3 (Blue) and W4 (Red). Top Right - The % of White matter hyperintensities (WMH) in ICV for the 3 waves. Bottom Left - The % of Normal Appearing White Matter (NAWM) in ICV for the 3 waves. Note that WMH was multiplied by 10 for ease of plotting. Ages at waves 2 to 4 are age 73, 76 and 79 respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2Association between sleep parameters and brain volume change from 73 to 79, given as β (p -value).

Brain volume slopes	Day-time sleep duration (hours)	Night-time sleep duration (hours)	Night sleep efficiency	Difficulty Awakening	Sleep Quality
TBV	-0.033 (0.671)	0.063 (0.389)	0.041 (0.619)	0.093 (0.197)	-0.050 (0.495)
GM	-0.035 (0.725)	-0.148 (0.154)	-0.072 (0.501)	0.112 (0.259)	-0.143 (0.167)
NAWM	-0.129 (0.050)	0.160 (0.011)	0.204 (0.009)	0.007 (0.907)	0.086 (0.172)
WMD	0.122 (0.018)	0.040 (0.421)	-0.044 (0.412)	0.003 (0.944)	-0.002 (0.962)
WMH	0.116 (0.026)	-0.004 (0.940)	-0.044 (0.417)	0.003 (0.945)	-0.034 (0.508)

Note. Values are the standardized β (P -value) of the association between sleep variables and change in brain volumes over a period of 6 years (age 73–79), corrected for sex and within-wave variance in age. All brain metrics were corrected for intracranial volume. WMH = White Matter Hyperintensities; WMD = White matter damage; TBV = total brain volume; GM = Grey matter volume; NAWM = Normal Appearing White Matter.

Fig. 1 shows that WMH increased and normal-appearing white matter (NAWM) and grey matter (GM) decreased from waves 1 to 3.

3.2. Sleep and brain structural health over time

As previously reported in this cohort [18,19], the sleep variables showed strong internal consistency; weekend and weekday sleep durations were highly correlated (e.g. at *night-time* Pearson $r = 0.970$, $P < 0.001$, [Supplementary Table S1](#), Cronbach's alpha 0.98). As such, we took the average of weekday and weekend measures for three of the sleep measures which we used in all subsequent analyses (daytime sleep duration, night time sleep duration, sleep efficiency).

Age- and sex-corrected associations (Model 2) between sleep measures and changes in brain measures are shown in [Table 2](#) and [Fig. 2](#) (intercepts reported in [Supplementary Table S2](#)). Shorter night time sleep duration was associated with steeper 6-year reduction of NAWM volumes ($\beta = 0.160$, $P = 0.011$). Longer day time sleep was associated with increasing white matter damage ($\beta = 0.122$, $P = 0.018$) and faster WMH growth ($\beta = 0.116$, $P = 0.026$). Lower sleep efficiency ($\beta = 0.204$, $P = 0.009$) was associated with greater NAWM volume loss from ages 73 to 79. These findings remained nominally significant with little-to-no attenuation of effect size when additionally corrected for vascular

risk factors (Model 2, [Fig. 2](#), [Supplementary Tables S3 and S4](#)), except that the association between longer daytime sleep duration and steeper NAWM volume loss (previously $p = 0.05$ in Model 1) was now also nominally significant ($\beta = -0.134$, $P = 0.043$). However, none of the associations shown in [Table 2](#) survived FDR correction. All models showed good fit to the data, and model fit indices for all models are presented in [Supplementary Tables S5–7](#).

3.3. PVS and brain structural health over time

Greater % of PVS in TBV were associated with lower volume of NAWM at age ~73 years ($\beta = -0.32$, $P < 0.001$, [Table 3](#)) and greater reduction in NAWM from age 73 to 79 ($\beta = -0.16$, $P = 0.012$). Similarly, increased % of PVS in TBV was associated with having more WMH at baseline ($\beta = 0.45$, $P < 0.001$) and greater WMH increase between ages 73 and 79 ($\beta = 0.42$, $P < 0.001$). Increased % of PVS in TBV was also associated with worse measures using the 'white matter damage metric' at age 73 ($\beta = 0.42$, $P < 0.001$) and between ages 73 and 79 ($\beta = 0.37$, $P < 0.001$). Similar associations were observed for PVS visual scores in the BG and CSO as for % of PVS in TBV ([Table 4](#)). All associations highlighted in bold typeface in [Tables 3 and 4](#) survived FDR correction (applied across all tests).

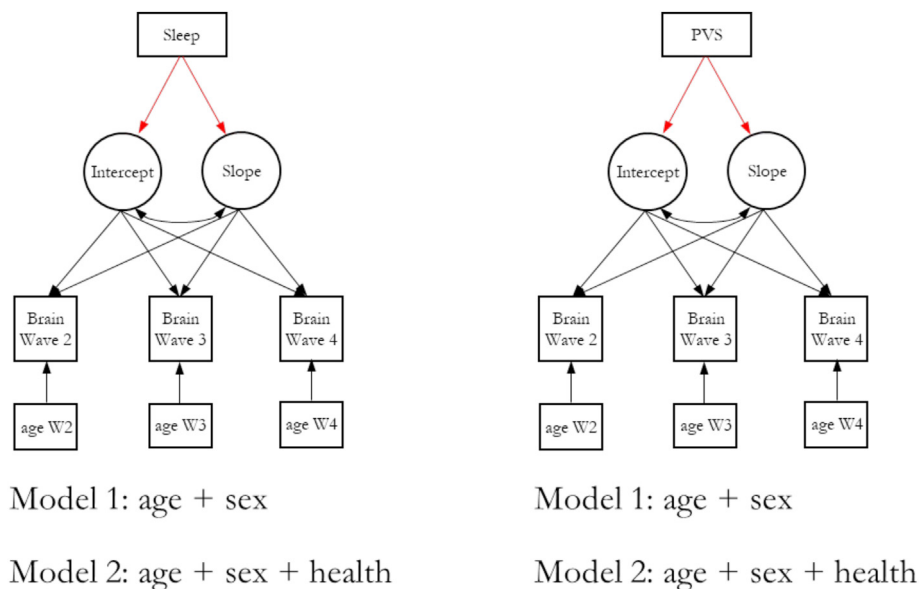


Fig. 2. Associations between brain structural changes and sleep measures. Levels and longitudinal changes in each brain imaging parameter (labelled "Brain") across three waves were estimated using latent growth curve models, corrected for within wave (scaled) age variance. Red paths indicate tests of interest. Additional covariates not shown. LEFT PANEL: Associations between sleep measures (assessed at Wave 3) and the level and change were assessed, corrected for sex (Model 1), and additionally for health covariates at wave 2 (self-reported diabetes, smoking, stroke, cardiovascular disease, hypertension, hypercholesterolaemia and BMI). A separate model was fitted for each sleep-MRI pairing. RIGHT PANEL: Associations between perivascular space (PVS) load measured at Wave 2 and intercept and slope of brain measures were analysed using the same model specification as above. Finally, in Model 3 (not shown), perivascular space (PVS) load was included as an additional covariate in Model 2 on the left panel, and the degree to which sleep-brain associations were attenuated was reported. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Association between PVS computational measures (volume and count) in the centrum semiovale, brain volumes at age 73, and brain volume change from 73 to 79, given as β (P-value).

Predictors	Total brain volume (TBV)			Grey matter			Normal-appearing white matter		
	PVS counts	PVS volume	% PVS volume in TBV	PVS counts	PVS volume	% PVS volume in TBV	PVS counts	PVS volume	% PVS volume in TBV
PVS	Intercept	-0.10(0.054)	-0.09(0.084)	-0.21(<0.0001)	-0.26(<0.0001)	-0.27(<0.0001)	-0.07(0.182)	-0.32(<0.0001)	-0.34(<0.0001)
	Slope	0.05(0.522)	0.01(0.943)	-0.02(0.789)	-0.12(0.166)	-0.08(0.353)	-0.05(0.44)	-0.16(0.018)	-0.17(0.01)
	Slope	-0.04(0.457)	-0.05(0.351)	-0.09(0.054)	-0.24(<0.0001)	-0.25(<0.0001)	-0.03(0.613)	-0.29(<0.0001)	-0.32(<0.0001)
PVS + COV	Intercept	0.08(0.301)	0.03(0.74)	0.03(0.745)	-0.10(0.277)	-0.09(0.328)	-0.06(0.377)	-0.16(0.016)	-0.16(0.012)
	Intercept								
	Slope								
Predictors	White matter hyperintensities			White matter damage					
	PVS counts	PVS volume	% PVS volume in TBV	PVS counts	PVS volume	% PVS volume in TBV	PVS counts	PVS volume	% PVS volume in TBV
PVS	Intercept	0.13(0.007)	0.44(<0.0001)	0.45(<0.0001)	0.45(<0.0001)	0.112(0.022)	0.412(<0.0001)	0.437(<0.0001)	0.437(<0.0001)
	Slope	0.17(0.001)	0.42(<0.0001)	0.42(<0.0001)	0.42(<0.0001)	0.127(0.008)	0.372(<0.0001)	0.374(<0.0001)	0.374(<0.0001)
	Slope	0.14(0.003)	0.44(<0.001)	0.45(<0.001)	0.45(<0.001)	0.114(0.019)	0.403(<0.001)	0.415(<0.001)	0.415(<0.001)
PVS + COV	Intercept	0.18(<0.001)	0.43(<0.001)	0.42(<0.001)	0.42(<0.001)	0.133(0.005)	0.375(<0.001)	0.37(<0.001)	0.37(<0.001)
	Intercept								
	Slope								

Note. Values are the standardized β (P-value) of the intercept and slope from SEM. Intercept represents level-level association i.e. association between PVS and brain volumes at baseline while slope represents association between PVS and change in brain volumes over time. TBV = total brain volume. COV are the covariates i.e. sex, age in days at scanning, and self-reported history of cardiovascular disease (y/n), hypertension (y/n), smoking (never, previously or current), hypercholesterolemia (y/n) and stroke (y/n, self-reported and found in images). The first model predicted brain volumes using PVS only. The second model predicted brain volumes using PVS and covariates.

3.4. Mediation of sleep-brain ageing associations by baseline PVS

Given that %PVS in TBV was consistently the strongest correlate of other brain levels and changes, and because it was the PVS measure that was most strongly associated with sleep measures (Supplementary Table S8), we selected this measure as a PVS metric for mediation analyses. For those five significant associations reported above between sleep and brain ageing, we examined whether any of that effect was attenuated by including PVS at baseline. Whereas only the association between daytime sleep duration and white matter loss was attenuated to non-significance ($\beta = -0.134$, $P = 0.043$ to $\beta = -0.127$, $P = 0.051$), the magnitude of the attenuation was extremely small (5.2%). The other four associations all remained nominally significant, and the associations magnitudes were, on average only ~5% mediated by %PVS in TBV. Full results are presented in Supplementary Table S9.

4. Discussion

In this large sample of community-dwelling individuals, the burden of enlarged PVS visible in the brain MRI examination at age ~73 years was associated with later worsening of white matter health, reflected as faster decrease in NAWM volume, greater increase in WMH and in the 'white matter damage metric' from years 73–79. Individuals who reported worse sleep efficiency and more daytime sleeping were those who also experienced significantly greater decline in their white matter health from ages 73 to 79, and our results show that this could be partly mediated by the PVS burden. Neither PVS burden, nor sleep quality or efficiency indicators were associated with deterioration in TBV or GM changes across the same period.

Several cross-sectional studies concur that sleep deprivation, quality and duration affect white matter health at the ages that have been examined so far [32–34]. A negative cross-sectional association between day-time sleepiness and white matter health has been reported previously [32], with another study in younger individuals concluding that inter-individual differences in white matter microstructure are related to habitual sleep patterns [32]. In middle age, a cross-sectional study found an association between insomnia and widespread reduction of mean and axial diffusivity in right hemisphere white matter tracts [33]. A previous cross-sectional study in our cohort at age 76 also found less efficient sleep being associated with white matter atrophy at the same age [5], and a study in 613 middle-age adults (mean age 45.4 years) reported that short sleep duration was associated with worse markers of white matter integrity: mean diffusivity and presence of WMH, assessed from MRI scans taken at the same time point [34].

However, longitudinal studies are less clear. A recent longitudinal analysis at 5 time points across 28 years in the same cohort identified four different trajectory groups with different average sleep durations ranging from approximately 5 to 8 h, but found no significant differences in white matter microstructure or grey matter volumes between the groups [35]. Another study in late adulthood [60–82 years old], found that poor sleep quality at the time of the MRI scan was associated with reduced global fractional anisotropy and increased global axial and radial diffusivity, although with small effect sizes. And the same study found that the number of times participants reported poor sleep quality over five time-points spanning a 16-year period prior to the scan, was not associated with these white matter measures, thus suggesting that only current sleep quality affected the white matter integrity [36]. Together with our study, these findings may indicate either a short-term effect of lack of sleep efficiency on white matter health in late adulthood, or that altered sleep patterns in older people may relate to underlying brain changes but do not necessarily cause the brain

Table 4Association between PVS visual scores (in both: basal ganglia and centrum semiovale), brain volumes at age 73, and brain volume change from 73 to 79, given as β (P-value).

Predictors	Predicted variable	Total brain volume (TBV)		Grey matter		Normal-appearing white matter	
		PVS scores in Basal Ganglia	PVS scores in Centrum Semiovale	PVS scores in Basal Ganglia	PVS scores in Centrum Semiovale	PVS scores in Basal Ganglia	PVS scores in Centrum Semiovale
PVS	Intercept	0.015(0.743)	-0.03(0.525)	-0.05(0.333)	-0.11(0.016)	-0.23(<0.0001)	-0.14(0.001)
	Slope	-0.11(0.176)	-0.00(0.981)	-0.11(0.202)	-0.07(0.364)	-0.17(0.007)	-0.09(0.13)
PVS + COV	Intercept	0.03(0.501)	-0.04(0.403)	-0.03(0.578)	-0.11(0.013)	-0.23(<0.001)	-0.15(0.001)
	Slope	-0.09(0.232)	-0.01(0.949)	-0.10(0.244)	-0.09(0.297)	-0.16(0.011)	-0.09(0.146)

Predictors	Predicted variables	White matter hyperintensities		White matter damage	
		PVS scores in Basal Ganglia	PVS scores in Centrum Semiovale	PVS scores in Basal Ganglia	PVS scores in Centrum Semiovale
PVS	Intercept	0.32(<0.0001)	0.20(<0.0001)	0.30(<0.0001)	0.18(<0.0001)
	Slope	0.24(<0.0001)	0.27(<0.0001)	0.26(<0.0001)	0.20(<0.0001)
PVS + COV	Intercept	0.32(<0.001)	0.20(<0.001)	0.30(<0.001)	0.18(<0.001)
	Slope	0.25(<0.001)	0.27(<0.001)	0.27(<0.001)	0.20(<0.001)

Note. Values are the standardized β (P-value) of the intercept and slope from SEM. Intercept represents level-level association i.e. association between PVS and brain volumes at baseline while slope represents association between PVS and change in brain volumes over time. COV are the covariates i.e. sex, age in days at scanning, and self-reported history of cardiovascular disease (y/n), diabetes (y/n), hypertension (y/n), smoking (never, previously or current), hypercholesterolemia (y/n) and stroke (y/n, self-reported and found in images). The first model predicted brain volumes using PVS only. The second model predicted brain volumes using PVS and covariates.

changes. It may be that the young brain is more resilient to adverse effects of sleep impairments than the older brain, consistent with many other insults.

Although the association between enlarged PVS and WMH has been reported [37], the current study suggests that, in addition, an increase in visible PVS (by volume, count or visual scores) also predicts the rate of white matter atrophy and white matter structural damage in late adulthood, although not of total brain and grey matter volume changes. However, caution must be exercised with regards to the apparent lack of association with grey matter and total brain tissue atrophy rates. The software used to generate grey matter volumes, FSL-FAST, although considered a gold standard for normal-appearing tissue segmentation, does not discriminate healthy from unhealthy grey matter, thus although we removed WMH and stroke lesions to obtain the final volumes, hippocampal lacunes, microinfarcts, PVS, and cortical microinfarcts were not accounted for, which may have played a role in the results, especially given the known association between PVS and other markers of cerebrovascular health [6].

The lack of association between sleep parameters and grey matter atrophy is less surprising. A study examining the sleep quality and quantity in relation to cortical changes found that self-reported sleep quality and sleep disturbances were related to thinning of the right lateral temporal cortex, with lower quality and more disturbances being associated with faster thinning [38]. It is important to note that although the associations reported here were corrected for multiple comparisons, the data violate an assumption of even this liberal correction approach – the various brain measures and sleep measures are correlated, and thus each test does not represent an entirely unique opportunity for a false discovery. As such, it may be an overly conservative correction; and therefore the associations reported in Table 2 are still interesting and worthy of replication and further investigation. Information on sleep apnoea was not collected, but in the medical records it was reported in only one participant.

Our study, to the best of our knowledge, is the first study exploring the combined association of two markers of brain waste clearance and declining brain tissue health in late adulthood, providing new insights into their contribution to age-related brain atrophy. The population-based Rotterdam Scan Study reported an association between sleep efficiency and PVS burden, mainly in the centrum semiovale [39], in agreement with previous findings [5,40]. Our comprehensive statistical analysis suggests that this association may mediate the effect of sleep efficiency on short-term

white matter health outcome and deterioration rate. The sample size, population-based design, and age-homogeneity within our study participants are also strengths that have been acknowledged previously. However, multicentre studies with MRI conducted at higher field strengths under research protocols that may provide better discrimination among brain indicators of vascular health would be recommended.

One of the limitations of our study is the fact that the sleep measures are self-reported. Quantitative measures of sleep would have been better and more reproducible. However, we used a standard and well validated questionnaire based approach which has been validated previously [17–19]. Additionally, our results showed statistically strong internal consistency. These, plus the robust statistical analysis approach suggest that our result is not only valid, but also reproducible. Another limitation is the time-point when the sleep measures were recorded. We recorded the sleep measures at age 76 years and measured brain variables at ages 73, 76 and 79 years. It would have been better to measure sleep variables at age 73 but this was not possible because our original study design did not include sleep measures, and sleep was introduced only at age 76 years. Sleep variables could change over time, but general facets of sleep are fairly stable traits over a reasonable (i.e. ~3 year) period of time. Evidence from a relevant review [41] shows that we would not expect substantial differences in various aspects of sleep composition across such a short period, even within older age where changes are slightly faster. That is, we could reasonably expect that individual differences in sleep measured three years apart would likely strongly correlate with those same measures if taken at the same time-point. In this respect, a large longitudinal study has indicated that self-reported sleep length reduces by 0.5–1 min per year [42]. The fact that the results we report here are in the expected direction and of comparable magnitude to other cross-sectional associations also support the validity of our analysis. Another limitation is the use of one time measurement of sleep parameter. Measures from multiple time-points will give more information on the association between sleep and brain health. However, our results show a potential association between sleep and brain health that could be further explored in future studies.

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CRedit authorship contribution statement

Benjamin S. Aribisala: Formal analysis, Investigation, Validation, Visualization, Writing - original draft, Writing - review & editing. **Maria del C. Valdés Hernández:** Data curation, Project administration, Software, Visualization, Writing - original draft, Writing - review & editing. **Judith A. Okely:** Formal analysis, Investigation, Writing - review & editing. **Simon R. Cox:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing - review & editing. **Lucia Ballerini:** Data curation, Software, Writing - review & editing. **David Alexander Dickie:** Data curation, Software, Writing - review & editing. **Stewart J. Wiseman:** Data curation, Writing - review & editing. **Renata L. Riha:** Investigation, Methodology, Validation, Writing - review & editing. **Susana Muñoz Maniega:** Data curation, Project administration, Writing - review & editing. **Ratko Radakovic:** Data curation, Writing - review & editing. **Adele Taylor:** Data curation, Writing - review & editing. **Alison Pattie:** Data curation, Writing - review & editing. **Janie Corley:** Data curation, Writing - review & editing. **Paul Redmond:** Project administration, Resources, Writing - review & editing. **Mark E. Bastin:** Conceptualization, Data curation, Funding acquisition, Supervision, Writing - review & editing. **Ian Deary:** Conceptualization, Funding acquisition, Methodology, Resources, Writing - review & editing. **Joanna M. Wardlaw:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing - review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2023.03.016>.

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