

Blood pressure-related white matter microstructural disintegrity and associated cognitive function impairment in asymptomatic adults

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ABSTRACT

Background and objectives We aimed to investigate the white matter (WM) microstructural/cytostructural disintegrity patterns related to higher systolic blood pressure (SBP), and whether they mediate SBP effects on cognitive performance in middle-aged adults.

Methods Using the UK Biobank study of community-dwelling volunteers aged 40–69 years, we included participants without a history of stroke, dementia, demyelinating disease or traumatic brain injury. We investigated the association of SBP with MRI diffusion metrics: fractional anisotropy (FA), mean diffusivity (MD), intracellular volume fraction (a measure of neurite density), isotropic (free) water volume fraction (ISOVF) and orientation dispersion across WM tracts. Then, we determined whether WM diffusion metrics mediated the effects of SBP on cognitive function.

Results We analysed 31 363 participants—mean age of 63.8 years (SD: 7.7), and 16 523 (53%) females. Higher SBP was associated with lower FA and neurite density, but higher MD and ISOVF. Among different WM tracts, diffusion metrics of the internal capsule anterior limb, external capsule, superior and posterior corona radiata were most affected by higher SBP. Among seven cognitive metrics, SBP levels were only associated with ‘fluid intelligence’ (adjusted $p < 0.001$). In mediation analysis, the averaged FA of external capsule, internal capsule anterior limb and superior cerebellar peduncle mediated 13%, 9% and 13% of SBP effects on fluid intelligence, while the averaged MD of external capsule, internal capsule anterior and posterior limbs, and superior corona radiata mediated 5%, 7%, 7% and 6% of SBP effects on fluid intelligence, respectively.

Discussion Among asymptomatic adults, higher SBP is associated with pervasive WM microstructure disintegrity, partially due to reduced neuronal count, which appears to mediate SBP adverse effects on fluid intelligence. Diffusion metrics of select WM tracts, which are most reflective of SBP-related parenchymal damage and cognitive impairment, may serve as imaging biomarkers to assess treatment response in antihypertensive trials.

INTRODUCTION

Blood pressure (BP) is a major risk factor for cerebrovascular disease.¹ Asymptomatic brain pathologies found in hypertensive people—such as lacunar infarction, cerebral

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In hypertensive individuals, subtle microstructural changes reflecting axonal damage are present even in the absence of macroscopic damage and serve as early warning signs of latent small vessel cerebrovascular disease and neuronal injury.

WHAT THIS STUDY ADDS

⇒ Higher systolic blood pressure is associated with white matter microstructural damage and axonal loss among asymptomatic middle-aged adults, which likely mediate the adverse effects of higher blood pressure on cognitive performance, and are most notable in the internal and external capsules.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Diffusion metrics of select white matter tracts may serve as neuroimaging biomarkers to assess treatment response and predict cognitive decline prevention in future antihypertensive trials.

small vessel disease and microbleeds—are associated with early mild cognitive impairments and dementia.¹ Studies suggested that lowering the BP may decrease the risk of cognitive impairment or dementia.² In the absence of treatment for advanced cognitive impairment and dementia, preventive strategies provide the best option to avoid or delay the progression of cognitive decline. Advanced neuroimaging techniques can elucidate the underlying neurobiology of cerebral injury associated with BP and cognitive impairment; and detect clinically and radiologically incipient disease.³

Diffusion tensor imaging (DTI) can detect microstructural white matter (WM) abnormalities even in normal appearing tissue, and preceding any visually conspicuous injury—that is, WM hyperintense (WMH) lesions.⁴ DTI metrics quantify water molecule displacement, which in the brain WM is greater parallel to axons than perpendicular to them.

Thus, DTI can probe into neurobiological mechanisms of axonal fibre injury.⁵ Specifically, lower fractional anisotropy (FA) and higher mean diffusivity (MD) indicate an overall reduction in WM fibre integrity.⁵ Multiple studies have investigated the association between DTI biomarkers and cognitive status, showing a clear relationship with both disease burden and risk.⁶ However, the conventional diffusion tensor model is unable to examine the underlying cerebral cytostructure; for example, lower FA may represent either neuron loss or increased dispersion of neural fibre orientation. Recently, multicompartment diffusion models have been proposed for more specific delineation of brain 'cytostructure' based on intracellular, extracellular and cerebrospinal fluid diffusion characteristics.⁷ The new multicompartment diffusion models are more sensitive to subtle cytoarchitectural changes than conventional DTI; and can determine whether lower FA is due to decreased axonal/neurite density (ND), crossing fibres (orientation dispersion, OD) or increased extracellular isotropic free water diffusion.⁵ Although prior studies reported that higher BP levels are associated with altered DTI metrics, there are scarce data on the topographic distribution of WM microstructural damage due to BP, the underlying cytostructural injury and how BP-related changes in diffusion metrics affect cognitive function.

In our work, we used data from more than 31 000 participants from the UK Biobank⁸ study to investigate the relationship of systolic BP (SBP) levels with diffusion metrics of microstructural integrity and cytostructural organisation across different WM tracts. Then, we explored whether WM tract microstructural disintegrity mediates the association between SBP levels and cognitive function. Our results determine the topology and microstructural/cytostructural underpinnings of BP-related WM injury and their relationship with cognitive outcome in a large cohort of asymptomatic middle-aged adults.

METHODS

Study design

We conducted a nested cross-sectional study within the UK Biobank, a population-based cohort study that enrolled 502 480 community-dwelling volunteers across the UK between 2006 and 2010.⁸ For this study, we included participants with available DTI neuroimaging data and no medical history of stroke, dementia, multiple sclerosis, demyelinating disorders or traumatic brain injury.

Neuroimaging protocol

A subset of UK Biobank participants consented to the imaging study. These participants underwent research-quality brain MRI using a Siemens Skyra 3-Tesla scanner, with a standard 32-channel radiofrequency receive head coil. Multishell diffusion scans were acquired at two b-values ($b=1000$ and 2000 s/mm²) at 2 mm isotropic spatial resolution with 50 distinct diffusion-encoding

directions at each of the two b-values. The scan duration was 7 min.⁹

BP measurements

In the UK Biobank study, two measurements of BP were taken by trained registered nurses using an automated Omron blood pressure monitor or a manual sphygmometer if the automated device could not be employed or if appropriately sized BP cuffs were unavailable. Participants were in a seated position, with feet parallel to each other flat on the floor, with no restrictive clothing to impede circulation to their left upper arm (right arm is used if left is not practical). In our analyses, we used the average of the first and second SBP measurements obtained during the imaging visit.

Covariates potentially affecting WM microstructure

We included age, sex, smoking status, body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), haemoglobin A1c and history of diabetes mellitus as covariates in regression models to adjust for confounding effects on WM microstructure and cytostructure.^{10–13} In additional sensitivity analysis, we adjusted for WMH volumes, antihypertensive medication intake and the educational level (which may theoretically affect cognitive function performance). Finally, to further reduce the likelihood of age acting as a confounder, we performed analyses separately for three age strata delimited by the 33rd and 67th percentile.

Diffusion metrics

We used neuroimaging metrics provided by the UK Biobank as reported previously.⁹ DTI metrics were calculated using DTIFIT, an FSL¹⁴ software tool enabling fitting of voxel-wise diffusion tensor models, and quantification of DTI metrics including FA and MD. In addition, the diffusion MRI data were fed into Neurite Orientation Dispersion and Density Imaging (NODDI) modelling,⁷ using the Accelerated Microstructure Imaging via Convex Optimisation tool¹⁵ to derive the following voxel-wise NODDI parameters: intracellular volume fraction (ICVF), isotropic (free) water volume fraction (ISOVF) and OD index. FA represents the directionality of water diffusion, MD characterises the overall diffusivity, ICVF estimates ND, ISOVF represents the free water fraction and OD reflects the overall coherence of fibres (0 for perfectly aligned straight fibres and 1 for completely isotropic fibre directions).⁷ All these metrics were calculated across 48 WM tracts defined in the 'ICBM-DTI-81' Johns Hopkins atlas.¹⁴

Cognitive function metrics

We analysed seven cognitive measures developed by the UK Biobank study which were ascertained at the time of the imaging visit (<https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100026>): (1) prospective memory, (2) pairs matching, (3) fluid intelligence, (4) reaction time, (5) symbol digit substitution, (6) trail making A and (7) trail making B. The details of these cognitive tests,

associated tasks, and scoring units are included in online supplemental table 1. Notably, despite the brief, non-standard nature of UK Biobank cognitive tests, a measure of general cognitive ability based on the UK Biobank tests has shown strong correlation with one created using standard reference cognitive tests.¹⁶

Statistical analysis

We present discrete variables as counts (percentages (%)) and continuous variables as mean (SD) or median (IQR), as appropriate. We used multiple linear regression to model the association between SBP levels and each DTI metric across the 48 WM tracts; where, DTI metric was defined as dependent variable, and independent variables included the SBP and covariates listed above. We also modelled the association between SBP and the seven cognitive metrics using univariate linear regressions, followed by mediation analysis to determine WM diffusion metrics which significantly mediate the association between SBP and cognitive measure, using the 'mediation' R package with non-parametric bootstrap CIs (1000 simulations) separately for each DTI metric. The variance inflation factor (VIF) was calculated to assess multicollinearity, assuming the presence of collinearity when VIF >5. For our primary analysis, we used Bonferroni-corrected p values to declare statistical significance (where $p < 0.05/$

(48 tracts*5 DTI metrics) ascertained significance). For secondary analyses looking at mediation, we first selected cognitive metrics that were significantly associated with SBP ($p < 0.05/7$ metrics), and then used 0.05/5 DTI metrics as the p value threshold to declare statistical significance. All analyses were performed using R V.4.0.¹⁷

RESULTS

Patients' demographics

Of the 502 480 participants enrolled in the UK Biobank, 40 653 had complete neuroimaging data available. From those, we excluded 9007 with missing data on BP or any of the adjustment covariates, 276 with stroke and 7 with dementia, resulting in the analytical sample size of 31 363 participants. The mean age was 63.8 (SD 7.7) years, and 16 523 (53%) were female. Baseline characteristics are summarised in table 1. Online supplemental table 2 compares the demographics of 31 363 participants who were included vs 9290 excluded from our analysis and shows that those who were included were slightly younger and more likely to be of European ancestry.

SBP and WM microstructure integrity

In our analysis, higher SBP was associated with indicators of WM disintegrity across several regions and DTI

Table 1 Baseline characteristics of the studied population

	Overall	Normal SBP	Elevated SBP	P value
n	31 363	15 913	15 450	
Age (years), mean (SD)	63.81 (7.66)	61.88 (7.60)	65.79 (7.21)	<0.001
Male sex, n (%)	14 840 (47.3)	6320 (39.7)	8520 (55.1)	<0.001
Ethnic background, n (%)				0.07
Asian	381 (1.2)	201 (1.3)	180 (1.2)	
Black	156 (0.5)	69 (0.4)	87 (0.6)	
Mixed	128 (0.4)	77 (0.5)	51 (0.3)	
Other	159 (0.5)	86 (0.5)	73 (0.5)	
White	30 459 (97.4)	15 435 (97.3)	15 021 (97.5)	
European ancestry, n (%)	27 444 (87.5)	13 758 (86.5)	13 684 (88.6)	<0.001
Smoking status, n (%)				<0.001
Never	19 155 (61.1)	10 039 (63.1)	9116 (59.0)	
Previous	10 288 (32.8)	4812 (30.2)	5476 (35.4)	
Current	1920 (6.1)	1062 (6.7)	858 (5.6)	
BMI (kg/m ²), mean (SD)	26.52 (4.17)	25.73 (3.93)	27.34 (4.25)	<0.001
SBP (mmHg), mean (SD)	138.7 (18.6)	125.1 (10.1)	152.6 (14.6)	<0.001
DBP (mmHg), mean (SD)	81.4 (9.9)	76.5 (7.3)	86.5 (9.5)	<0.001
LDL-C (mmol/L), mean (SD)	3.59 (0.83)	3.51 (0.81)	3.66 (0.84)	<0.001
Haemoglobin A1c (%), mean (SD)	5.35 (0.46)	5.31 (0.43)	5.39 (0.48)	<0.001
Atrial fibrillation, n (%)	895 (2.9)	392 (2.5)	503 (3.3)	<0.001
Diabetes mellitus, n (%)	1155 (3.7)	448 (2.8)	707 (4.6)	<0.001

Elevated SBP was defined as ≥ 140 mm Hg.
 BMI, body mass index; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

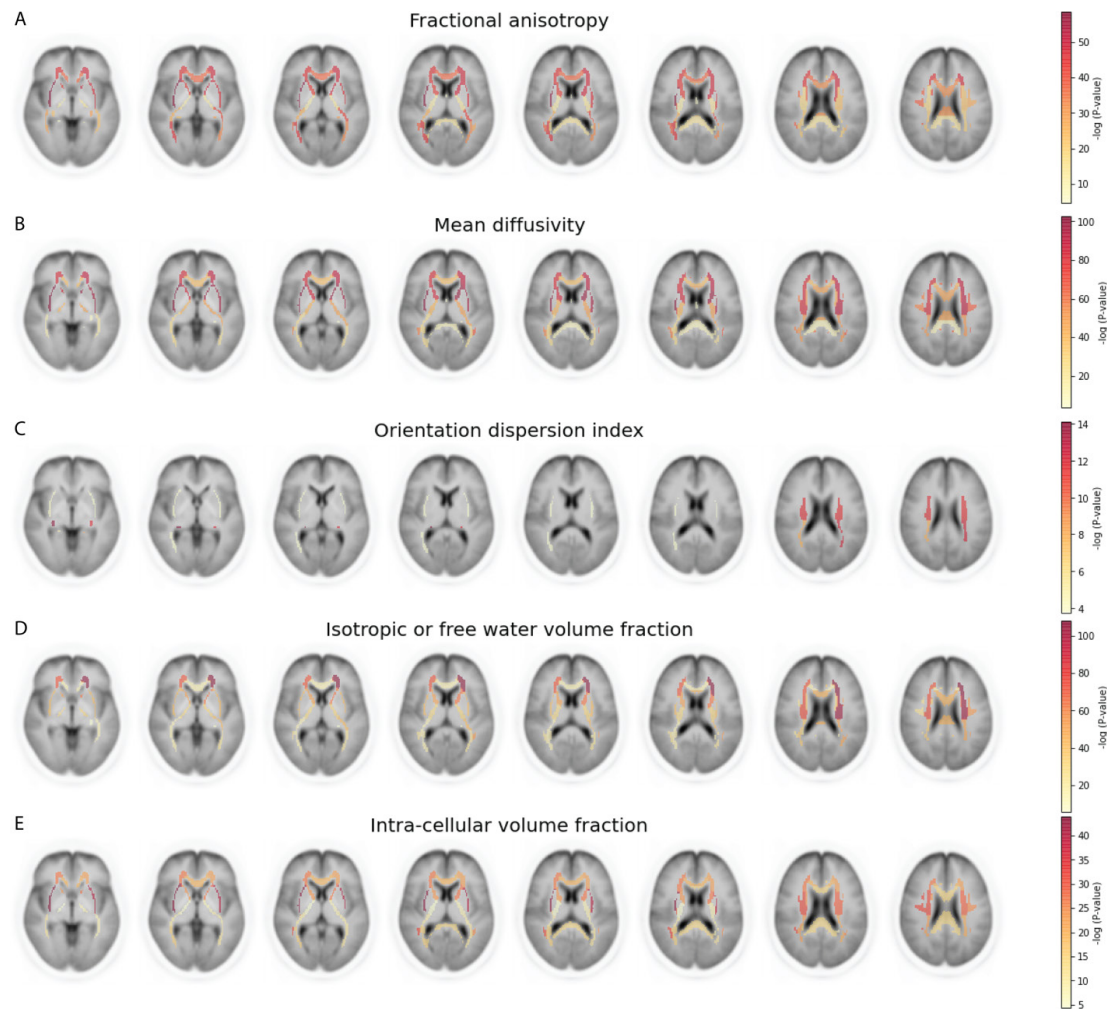


Figure 1 Statistical significance from association analyses results between systolic blood pressure and diffusion metrics across white matter (WM) tracts. (A) Fractional anisotropy, (B) Mean diffusivity, (C) Orientation Dispersion Index, (D) Isotropic (free) water volume fraction, and (E) Intracellular volume fraction—a measure of neurite density. The colour bars represent $-\log$ 10 p values from multivariable regression models. Only WM tracts reaching significance after Bonferroni correction are coloured.

metrics—namely, lower FA and ICVF, higher MD and ISOVF, and higher or lower OD depending on the region (figures 1 and 2). Notably, the topographic extents of changes in FA, MD, ICVF and ISOVF in relation to SBP were more pervasive compared with OD (figures 1 and 2). Ten mm Hg increase in SBP was associated with decreases in FA ranging from 0.5% to 1.5%, and increases in MD ranging from 0.5% to 2.2% (figures 2 and 3). Among different WM tracts, the anterior limb of the internal capsule, the external capsule, the superior and posterior corona radiata consistently demonstrated significant changes in most DTI metrics in relation to higher SPB (figures 1–3). We found similar patterns after adjusting for the WMH volumes, antihypertensive medication intake and educational level (online supplemental figures 1–6). In addition, similar results were achieved when analysis was performed in three separate age strata delimited by the 33rd and 67th percentile (online supplemental figures 7–12). There was no indication of collinearity between covariates in any of the models (all VIF <5).

WM diffusion metrics mediate the relationship of SBP and cognitive function

Among the seven different metrics of cognitive function, ‘fluid intelligence’ was the only variable showing significant association with SBP after applying Bonferroni correction (table 2). To determine whether the effect of SBP on fluid intelligence was mediated by changes in WM integrity, we conducted mediation analysis. We found that the SBP effect on fluid intelligence was indeed mediated by changes in several DTI metrics across multiple WM tracts (figures 4 and 5). Specifically, microstructural disintegrity in the external capsule and the anterior limb of the internal capsule, along with the superior cerebellar peduncle and the stria terminalis, mediated the effects of SBP on fluid intelligence (figures 4 and 5). Of note, the average FA of external capsule, anterior limb of the internal capsule, and superior cerebellar peduncle mediated 13%, 9% and 13% of the effect of SBP on fluid intelligence, respectively. And, the average MD of external capsule, anterior limb of the internal capsule, posterior



Figure 2 (A) Statistical significance from association analyses results between systolic blood pressure (SBP) and diffusion metrics across white matter tracts. The colour bars represent p values from multivariable regression models. Only p values reaching significance after Bonferroni correction are coloured. (B) Average percentage change in DTI metrics for each 10 mm Hg increase in SBP across white matter tracts. The colour bars represent the percentage change. Only values reaching significance after Bonferroni correction are coloured. DTI, diffusion tensor imaging; FA, fractional anisotropy; ICVF, intracellular volume fraction; ISOVF, isotropic (free) water volume fraction; MD, mean diffusivity; SBP, systolic blood pressure.

limb of the internal capsule, and superior corona radiata mediated 5%, 7%, 7% and 6% of the effects of SBP on fluid intelligence, respectively. Results remained unchanged after adjusting for educational level (online supplemental figure 13).

DISCUSSION

In a large cross-sectional study, we analysed the association between the SBP, brain WM microstructural integrity and BP-related cognitive changes among asymptomatic middle-aged adults without a history of cerebrovascular disease or dementia. We found that higher SBP levels are associated with pervasive microstructural disintegration in WM tracts. This was likely related to decrease in nerve fibre count (lower ICVF—a measure of ND) and associated increase in free water fraction (ISOVF) in these WM tracts. Specifically, there were significant SBP-related abnormalities in most diffusion metrics of the internal capsule anterior limb, external capsule, anterior and superior corona radiata. Of note, these associations

were established after correcting for age, sex, smoking status, BMI, serum LDL-C, HbA1c and history of diabetes mellitus; with similar results across different age strata, and after correcting for WMH volumes, antihypertensive medication use and educational levels. We also found that higher SBP is associated with worse fluid intelligence performance among different metrics of cognitive function available in the UK Biobank. In mediation analysis, the SBP-related impairment of fluid intelligence was mediated by microstructural disintegration and reduced ND across multiple WM tracts—in particular, the internal capsule anterior limb and external capsule. Diffusion metrics of these WM tracts may serve as neuroimaging markers of hypertension-related cerebral microstructural damage and associated cognitive decline.

Previous studies explored the relationship of BP-levels with increased WMH volume,^{18 19} and changes in WM microstructure.^{20 21} Subtle changes reflecting demyelination or axonal degeneration may present in the absence of macroscopic damage and serve as early warning signs

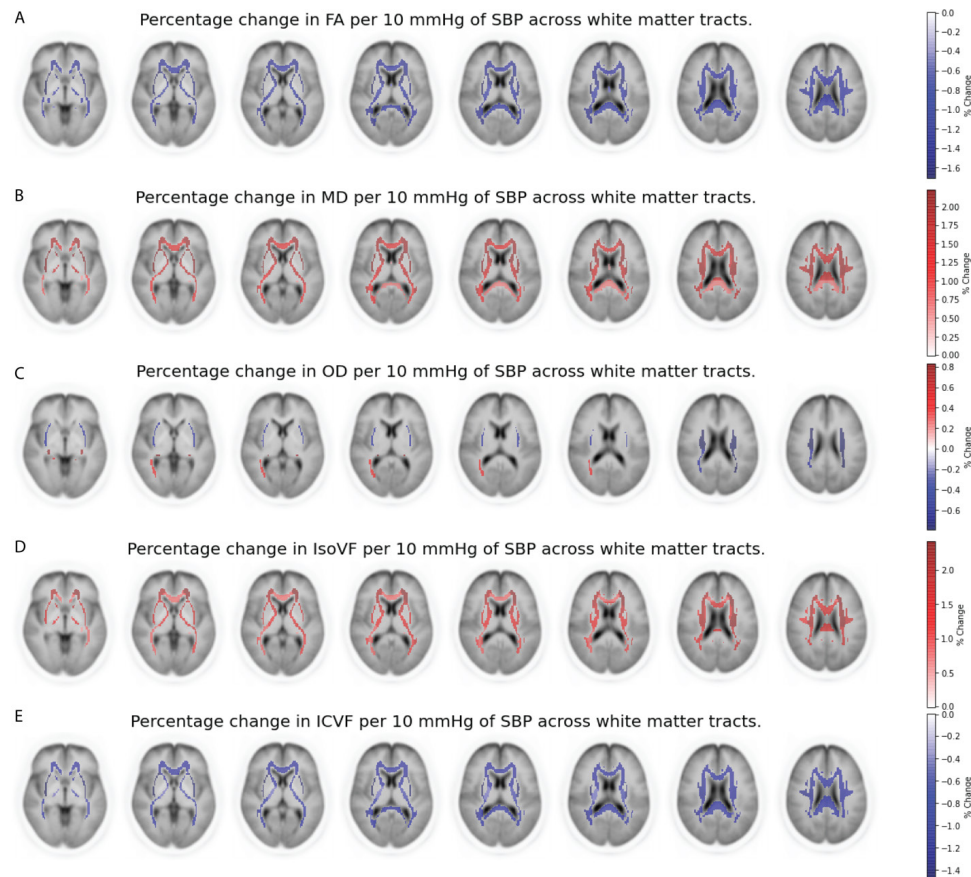


Figure 3 Average percentage change in DTI metrics for each 10 mm Hg increase in systolic blood pressure (SBP) across white matter (WM) tracts: (A) Fractional anisotropy (FA), (B) mean diffusivity, (C) Orientation Dispersion (OD) Index, (D) Isotropic (free) water volume fraction (ISOVF) and (E) Intracellular volume fraction (ICVF)—a measure of neurite density. Red colour represents positive association and blue colour represents negative association. Only WM tracts reaching significance after Bonferroni correction are coloured.

of latent vascular pathology.²² DTI can detect microstructural abnormalities and axonal fibre damage preceding the formation of WMH lesions.⁴ In this study, we evaluated a large cohort of asymptomatic adults who underwent multishell diffusion imaging to identify the topologic pattern of WM injury, and pinpoint the underlying cytostructural mechanism.⁵ While BP-related WM

microstructural injury was pervasive, we found stronger associations in key areas such as the anterior limb of the internal capsule, the external capsule and the anterior and superior corona radiata, with the highest percentage of diffusion metrics change per 10 mm Hg SBP increase (figure 3). In addition, the BP-related WM microstructural disintegrity marked by increased water molecule diffusivity (lower FA and higher MD) is likely related to a reduced number of neuronal elements in WM tracts as suggested by lower ICVF and higher ISOVF. The WM tract OD changes in relation to SBP were variable across different regions. This is because neuronal loss sparing parallel fibre tracts will reduce both OD and ND (ie, ICVF); whereas, neuronal loss with selective loss of parallel fibre or unidirectional organisation of fibre elements will lead to higher OD but lower ND. Thus, our results suggest that the underlying mechanism of WM tract microstructural disintegrity related to higher SBP is neuronal loss rather than worsening neural fibre organisation (ie, OD).

Subcohort analysis of 560 participants (≥ 50 years of age) from the 1000BRAINS study demonstrated the association of high SBP and diastolic BP with WMH volume, with SBP showing a stronger association than diastolic BP.¹⁹ They also found that periventricular WMH—more

Table 2 Association results between systolic blood pressure and measures of cognitive function available in UK Biobank

Cognitive outcome	Beta	SE	P value
Prospective memory	−0.01	0.009	0.28
Pairs matching	−0.001	0.002	0.73
Fluid intelligence	−0.05	0.007	<0.001
Reaction time	−0.08	0.34	0.81
Symbol digit substitution	−0.038	0.02	0.04
Trail making A	0.002	0.003	0.43
Trail making B	0.008	0.005	0.08

Bonferroni corrected p value significance threshold: 0.0071. Statistically significant differences are marked with bold text.

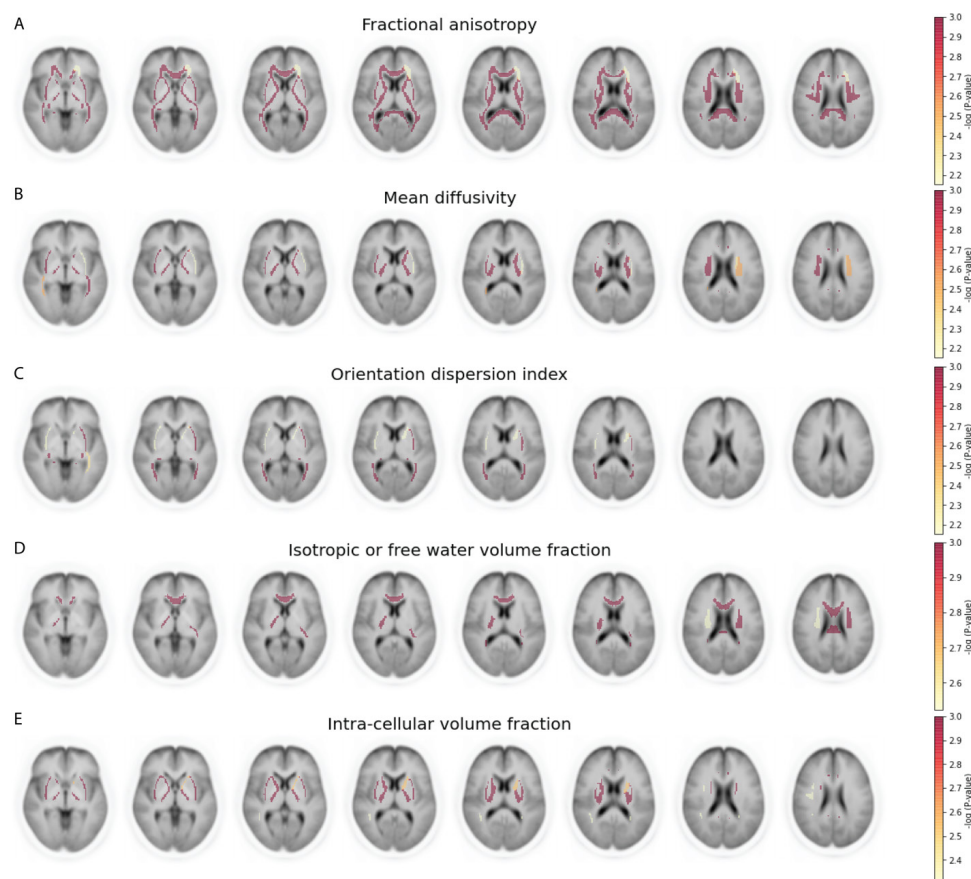


Figure 4 Statistical significance from mediation analyses results depicting DTI metrics which significantly mediated the effects of systolic blood pressure on fluid intelligence across white matter (WM) tracts. (A) Fractional anisotropy, (B) mean diffusivity, (C) Orientation Dispersion Index, (D) Isotropic (free) water volume fraction and (E) Intra-ellular volume fraction—a measure of neurite density. The colour bars represent $-\log_{10} p$ values from mediation analyses. Only WM tracts reaching significance after Bonferroni correction are coloured. DTI, diffusion tensor imaging.

so than deep WMH lesions—mediated the association between SBP and cognitive performance.¹⁸ We found a similar association of WM microstructural disintegrity with higher SBP, which also mediated the effect of SBP on fluid intelligence—even after correcting for total WMH volume (online supplemental figures 1–3). Our study supports the notion that visually inconspicuous but quantitative diffusion changes in WM tracts may better reveal which individuals are at higher risk of hypertension-related cognitive impairment.⁶ Although these associations were numerically small—for example, 10 mm Hg increase in SBP was associated with FA decreases ranging from 0.5% to 2.2% and mediation effects ranging from 5% to 13%—they can guide optimal sample size calculation in future trials where WM diffusion metrics serve as potential imaging markers and quantifiable endpoints for BP lowering interventions.^{23 24}

Although hypertension-related cognitive impairment has been reported previously,²⁵ a causal association is still difficult to establish and results from randomised clinical trials have been equivocal.²⁵ A meta-analysis of randomised clinical trials published in 2020 found that lowering BP with antihypertensive agents compared with control is associated with a lower incidence of

dementia or cognitive impairment.²⁶ However, another meta-analysis found no difference between intensive (ie, lower than usual) BP reduction versus standard management in decreasing the incidence of dementia and cognitive decline.²⁷ Secondary analysis of a clinical trial also suggested that BP lowering may be associated with specific subtypes of cognitive decline, such as amnesic and multidomain mild cognitive impairment.²⁸ Similarly, in our study, among different measures of cognitive function, SBP levels were negatively associated with fluid intelligence scores. Fluid intelligence represents verbal-numeric reasoning and is pivotal in adapting to new circumstances without prior knowledge.²⁹ Importantly, our study suggests that SBP levels could exert their effect on cognitive function by damaging WM microstructure, providing support for a causal mechanism behind this relationship. Of note, loss of neuronal elements (lower ICVF or ND) appears to be the underlying neurobiological mechanism mediating the BP-related cognitive impairment. Particularly, the diffusion metrics of external capsule and anterior limb of the internal capsule WM tracts had the highest percentage mediation of BP-related cognitive impairment and may provide potential therapeutic targets for future antihypertensive treatment trials.

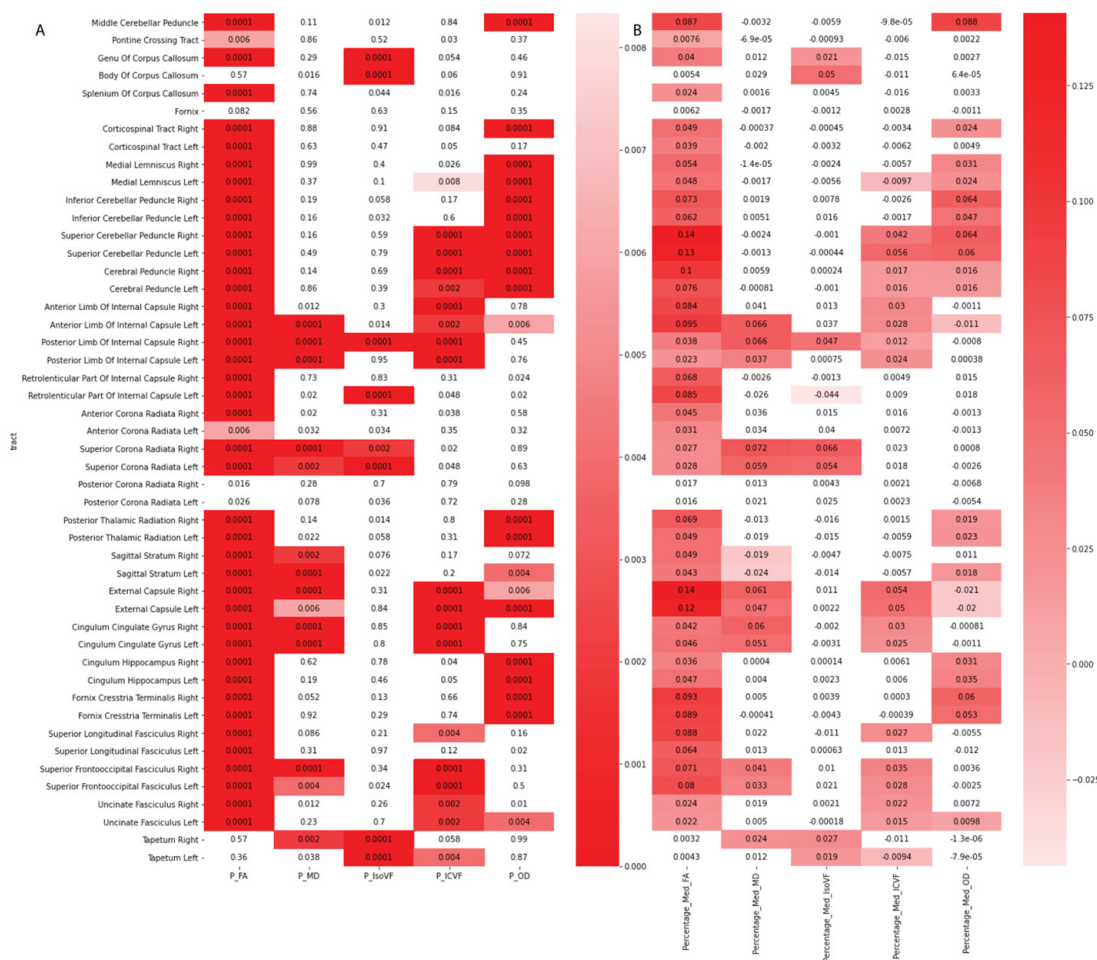


Figure 5 (A) Mediation analyses results with diffusion metrics highlighted which significantly mediated the effects of systolic blood pressure (SBP) on fluid intelligence across white matter (WM) tracts. Colour bars represent p values from mediation analyses. Only p values reaching significance after Bonferroni correction are highlighted. (B) Average mediated effects proportion of SBP through WM tract diffusion metrics on fluid intelligence. Colour bars represent the average mediated effects proportion. Only average mediated effects associated with p values reaching significance after Bonferroni correction are highlighted. FA, fractional anisotropy; ICVF, intracellular volume fraction; ISOVF, isotropic (free) water volume fraction; MD, mean diffusivity; OD, ISOVF.

Our findings specifically identified those WM tracts, where microstructural integrity had the highest mediation effects in the relationship between higher SBP and worse fluid intelligence—namely, the external capsule and anterior limb of the internal capsule. Previous DTI studies have also shown that higher fluid intelligence scores are associated with WM microstructural integrity in specific brain regions.³⁰ Specifically, FA values in the superior longitudinal fasciculus—an association tract connecting frontal, parietal, temporal and occipital lobes—have been linked with fluid intelligence.³¹ In multi-modal MRI of 547 middle-aged adult participants in the stage 2 Cambridge Centre for Ageing and Neuroscience study, the FA of the anterior corona radiata and external capsule contributed to both visual working memory and fluid intelligence.³² The DTI metrics of microstructural integrity in these select WM tracts can serve as potential therapeutic targets in antihypertension trials, and may

reflect treatment response before manifestation of long-term functional outcome benefits.

Many studies highlighted WM microstructural disintegrity as a fundamental aspect of normal age-associated cognitive decline and dementia.⁶ Indeed, the associations between WM microstructure and executive functions or processing speed are also found in regions outside of WM signal abnormality—that is, normal appearing WM.^{21 22} In addition, there is accumulating evidence that even mildly elevated BP within the normotensive range may affect cognitive functioning.^{20 21} By analysing the BP range instead of binary or multilevel categorisation of hypertension, we could capture the effects of BP across the whole spectrum on WM microstructure and cognitive function. Our findings in asymptomatic adults, and prior reports portend a role for neuroimaging markers of WM microstructure and cytostructure integrity to assess treatment response in antihypertensive trials as a surrogate

for late-onset cognitive decline. Of note, a previous power calculation study in patients with cerebral small vessel disease indicated that difference detection for DTI parameters requires much smaller sample sizes than lacunar infarcts, due to the low frequency of new lacunar stroke.³³ Our study pinpoints WM tracts where diffusion metrics may serve as therapeutic targets and tools of assessing treatment response in future clinical trials aiming to prevent/delay BP-associated cognitive decline.

Thus far, BP lowering trials showed no or only trivial reduction in progression of WMH volumes or DTI measures of microstructural disintegrity in response to treatment. In the INFINITY trial of hypertensive individuals >75 years old without a history of stroke, intensive BP lowering was associated with lower increase in WMH volumes (0.29%) compared with standard treatment (0.48%) over a 3-year period.³¹ In a subset analysis of 449 hypertensive adults >50 years old without a history of diabetes or stroke from the SPRINT trial, intensive BP lowering was also associated with lower increase in WMH volume (0.54 cm³ between-group difference) over a median intervention period of 3.40 years.³² The PROGRESS trial showed patients with a history of stroke who received BP lowering treatment had lower new WMH lesion volume (0.4 mm³) compared with a placebo group (2.0 mm³) over a 3-year period.³³ Finally, while intensive BP lowering over 2 years was not associated with significant differences in DTI markers in the initial analysis of the PRESERVE trial,³⁴ additional post-hoc brain network analysis detected treatment effects with network integrity improvements among those who received intensive BP lowering.³⁵ The clinical relevance of such small effect sizes remains equivocal. However, if validated in prospective trials, our results may help pinpoint which WM tracts exhibit more striking DTI changes in response to BP reduction, and are most relevant to long-term cognitive outcome.

Our study has a number of strengths, including the use of open access data from a large study, and the consistency of results across several DTI metrics. Importantly, postprocessing of brain MRI scans and extraction of diffusion metrics can be done automatically with existing pipelines, making average diffusion metrics reliably reproducible across different centres³⁴ and a good candidate as a neuroimaging marker of hypertension-related brain damage. Our work also has limitations, including the cross-sectional nature of the analysis, overall low ethnic diversity of the UK Biobank cohort, and selection bias as the community-dwelling volunteer participants in UK Biobank who consented to the imaging study might not be representative of the population. There is also growing evidence of associations between markers of WM injury and genes related to hypertension in young individuals even before they develop hypertension, suggesting a more fundamental premorbid relationship between WM microstructural pathologies and genetic risk of hypertension.^{35 36} Similar to prior studies,³⁷ we also only focused on SBP in our analysis, since SBP measurements are

highly correlated with diastolic and mean arterial pressure. Indeed, both higher SBP and diastolic BP are associated with mild cognitive dysfunction.³⁸ However, some studies could only detect association of SBP—and not the diastolic BP—with imaging metrics of brain age, WMH lesion volumes, and WM microstructural integrity.^{39 40} Of note, our mediation analysis only explored whether WM diffusion metrics—at least partially—mediated the association of SBP with fluid intelligence scores, as examination of all potential factors contributing to cognitive function would be beyond the scope of this study. Although sensitivity analysis showed similar results after adjustment for antihypertensive medication, our cross-sectional analysis cannot differentiate potential differences between untreated hypertension, undertreated hypertension or normal BP under treatment.

In summary, we found that among asymptomatic middle-aged adults, higher SBP is associated with pervasive WM microstructural disintegrity likely due to neuronal loss. We also showed that WM disintegrity may mediate the BP-related cognitive decline in this population. Furthermore, we pinpointed the specific WM tracts where diffusion metrics had the strongest association with SBP increase and had the highest percentage mediation of BP-related cognitive impairment. Overall, our findings characterise the topologic pattern of BP-related parenchymal damage and associated cognitive impairment, infer the underlying cytostructural mechanism and provide potential biomarkers to assess treatment response in future BP reduction trials.

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Contributors Conception and design of the study: JNA, SPH, GJF and SP. Acquisition and analysis of the data: JNA, SPH, CR, ACL, KNS, GJF and SP. Drafting of the manuscript and preparation of tables: JNA, SPH, CR, ACL, KNS, GJF and SP. SP accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The UK Biobank received approval from the National Information Governance Board for Health and Social Care (NIGB), the Community Health Index Advisory Group (CHIA), and the National Health Service North West Multi-centre Research Ethics Committee (MREC), and all participants provided informed consent through electronic signature at their baseline assessment (see also: <https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics>). We performed post-hoc analyses of deidentified patient data which was accessed using project application number 58743. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. The clinical and imaging data analysed in our study is available to researcher via the UK Biobank on completion of the registration process (see <https://www.ukbiobank.ac.uk/enable-your-research/register>) and on successful application (see <https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access>).

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