

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

SUPPLEMENTAL MATERIAL

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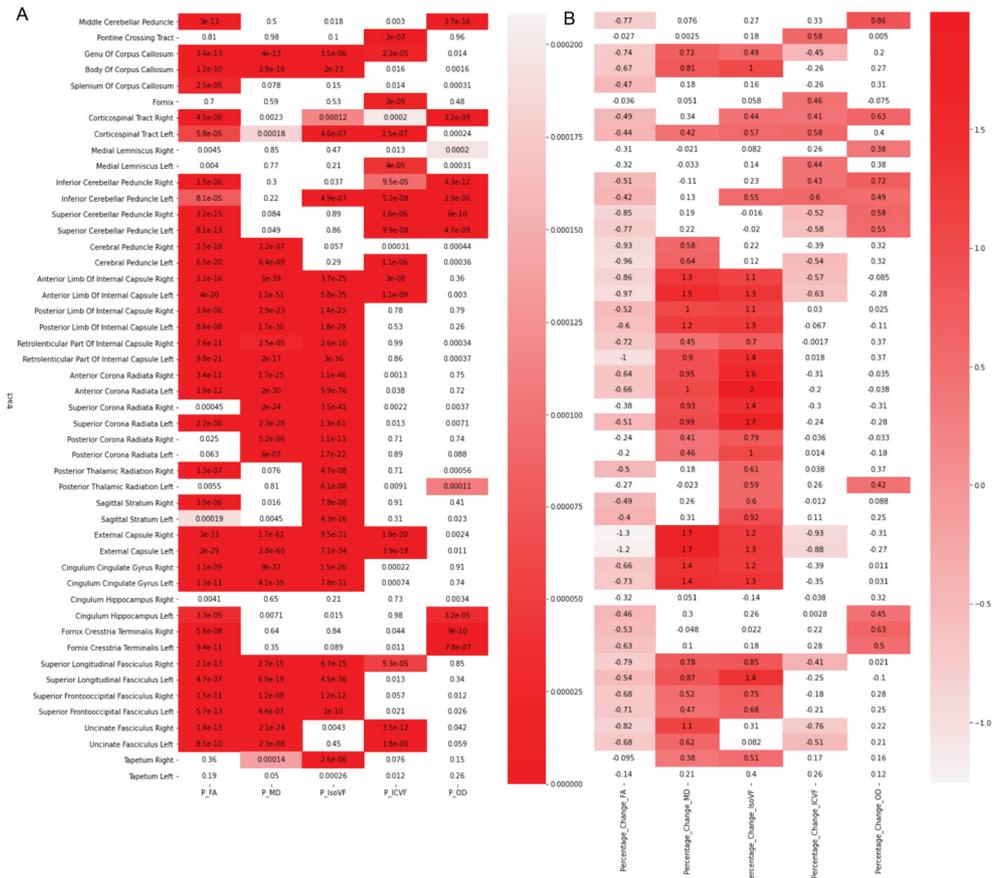
Supplemental Table 1. UK Biobank cognitive function tests performed at the imaging visit.

Cognitive measure	Description
Prospective memory	Participants were prompted with the following task: "At the end of the games we will show you four colored shapes and ask you to touch the Blue Square. However, to test your memory, we want you to actually touch the Orange Circle instead." We coded those who completed the task on the first attempt as 1 and the rest as 0.
Pairs matching	Participants are asked to memorize the position of as many matching pairs of cards as possible in the fewest tries. Up to three rounds were conducted; we used the second round for our analyses (6 pairs of cards). The final variable comprises the natural log-transformed number of incorrect matches (+1).
Fluid intelligence	Participants were tasked with answering as many questions as possible from a pool of 13 verbal logic/reasoning type multiple choice questions within two minutes. We used the total number of correct answers (maximum 13) in our analyses.
Reaction time	Participants are shown two cards at a time; if both cards are the same, they must press a button as quickly as possible. The test is based on twelve rounds, and, in our analyses, we use the mean time to correctly identify matches (maximum 2000 sec).
Symbol digit substitution	Participants were presented with one grid linking symbols to single-digit integers, and a second grid containing only the symbols, are asked to indicate numbers attached to each symbol in the second grid using the first one as a key. In our analyses, we used the number of correct substitutions, truncating values to the range 1 - 40 to exclude outliers.
Trail making A	Participants are tasked with connecting circles containing a sequence of numbers. We use the log-transformed time taken to complete this task (+1) in our analyses.
Trail making B	Participants are asked to connect circles containing numbers or letters by alternating between them in ascending sequence. We use the natural log-transformed time taken to complete this task (+1) in our analyses.

Supplemental Table 2. Demographics of UK Biobank participants with neuroimaging who were included in the analysis (n=31,363) versus those excluded due to missing data or pre-existing illness (n=9290).

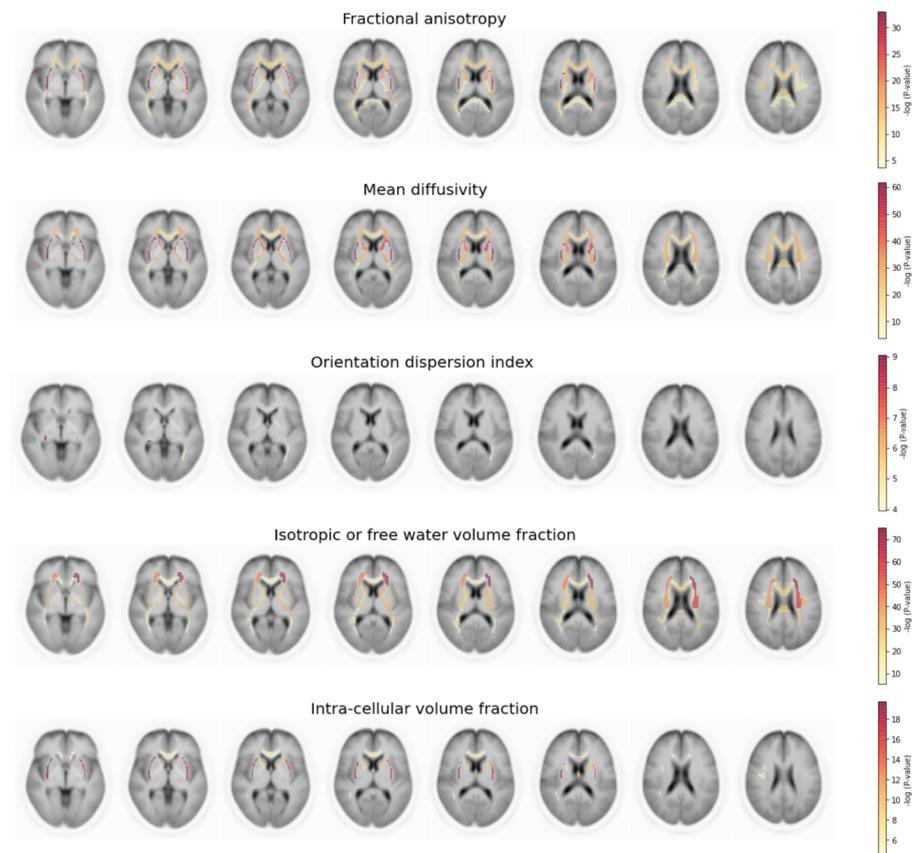
	Overall (n=40653)	Excluded (n=9290)	Included (n=31363)	p
Age [years], mean (SD)	63.95 (7.68)	64.43 (7.72)	63.81 (7.66)	<0.001
Male sex, n (%)	18676 (47.1)	3836 (46.1)	14840 (47.3)	0.055
Ethnic background, n (%)				<0.001
Asian	537 (1.3)	156 (1.7)	381 (1.2)	
Black	263 (0.6)	107 (1.2)	156 (0.5)	
Mixed	185 (0.5)	57 (0.6)	128 (0.4)	
Other	224 (0.6)	65 (0.7)	159 (0.5)	
White	39338 (97.0)	8879 (95.8)	30459 (97.4)	
European ancestry, n (%)	34510 (84.9)	7066 (76.1)	27444 (87.5)	<0.001
Smoking status, n (%)				0.665
Never	24758 (61.0)	5603 (60.9)	19155 (61.1)	
Previous	13299 (32.8)	3011 (32.7)	10288 (32.8)	
Current	2507 (6.2)	587 (6.4)	1920 (6.1)	
BMI [kg/m²], mean (SD)	26.52 (4.20)	26.50 (4.29)	26.52 (4.17)	0.712
SBP [mmHg], mean (SD)	138.7 (1.86)	138.7 (1.87)	138.7 (1.86)	0.95
DBP [mmHg], mean (SD)	81.4 (0.99)	81.3 (0.99)	81.4 (0.99)	0.356
LDL-C [mmol/L], mean (SD)	3.59 (0.83)	3.59 (0.83)	3.59 (0.83)	0.77
HbA1c [%], mean (SD)	5.35 (0.46)	5.36 (0.49)	5.35 (0.46)	0.17
Atrial fibrillation, n (%)	1155 (2.8)	260 (2.8)	895 (2.9)	0.807
Hypertension, n (%)	6459 (15.9)	1461 (15.7)	4998 (15.9)	0.639
Diabetes mellitus, n (%)	1498 (3.7)	343 (3.7)	1155 (3.7)	0.991

Supplemental Figure 1. Statistical significance and effect size of association between systolic blood pressure and white matter tracts diffusion metrics, adjusted for total white matter hyperintensities volume.



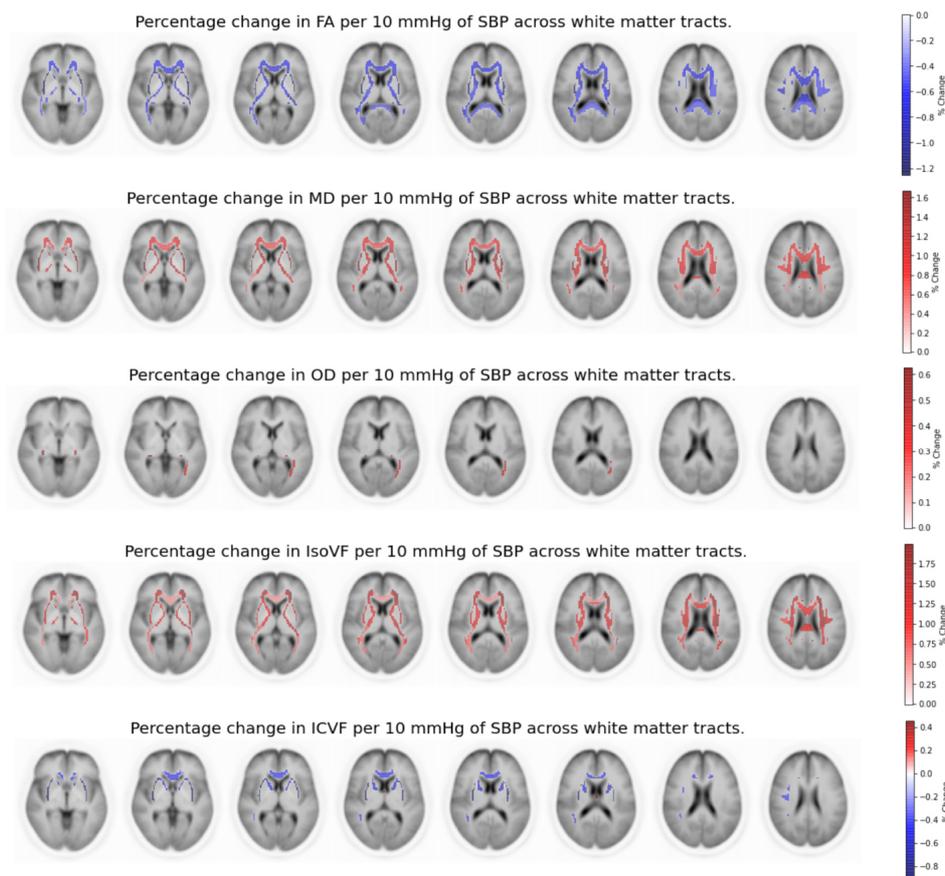
Supplemental Figure 1. (A) Statistical significance from association analyses results between systolic blood pressure (SBP) and diffusion metrics across white matter tracts, adjusted for total white matter hyperintensities volume. The color bars represent p-values from multivariable regression models. Only p-values reaching significance after Bonferroni correction are colored. (B) Average percentage change in DTI metrics for each 10 mmHg increase in systolic blood pressure across white matter tracts, adjusted for total white matter hyperintensities volume. The color bars represent the percentage change. Only values reaching significance after Bonferroni correction are colored.

Supplemental Figure 2. Topographic association of systolic blood pressure with white matter tracts diffusion metrics, adjusted for total white matter hyperintensities volume.



Supplemental Figure 2. Statistical significance from association analyses results between systolic blood pressure (SBP) and diffusion metrics across white matter (WM) tracts, adjusted for total white matter hyperintensities volume: (A) Fractional anisotropy, (B) Mean diffusivity, (C) Orientation dispersion index, (D) Isotropic (free) water volume fraction, and (E) Intra-cellular volume fraction – a measure of neurite density. The color bars represent $-\log_{10}$ p-values from multivariable regression models. Only WM tracts reaching significance after Bonferroni correction are colored.

Supplemental Figure 3. Percentage change in white matter tracts diffusion metrics per 10 mmHg increase in systolic blood pressure, adjusted for total white matter hyperintensities volume.



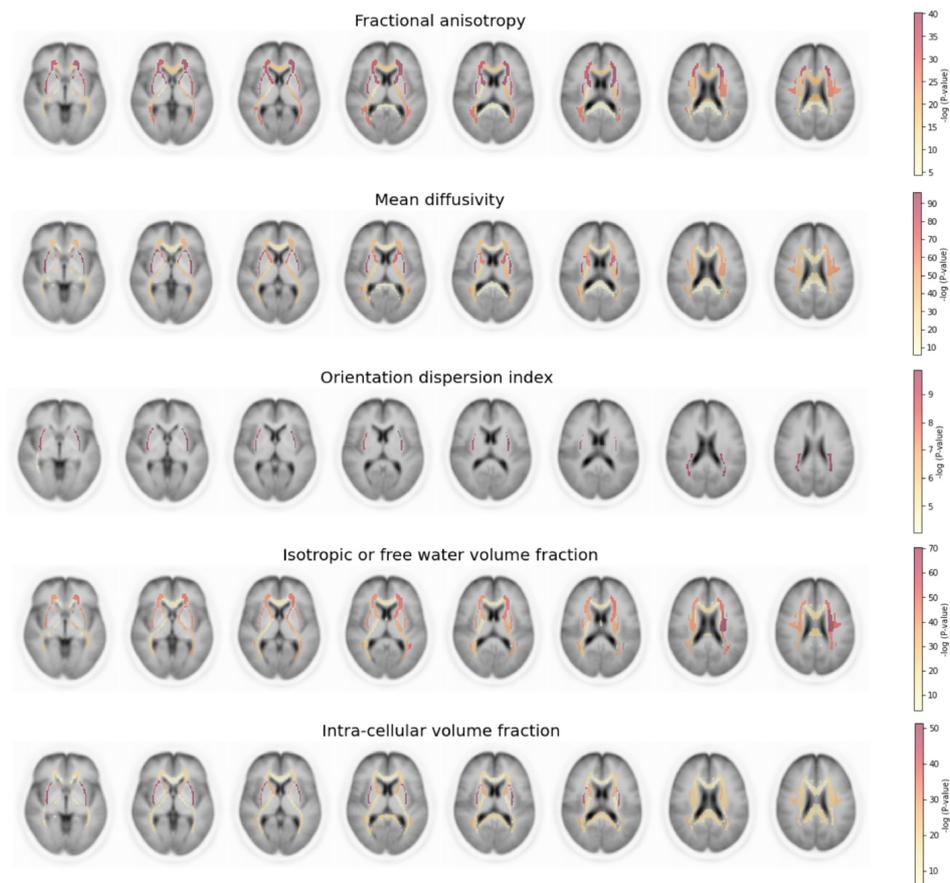
Supplemental Figure 3. Average percentage change in DTI metrics for each 10 mmHg increase in systolic blood pressure (SBP) across white matter (WM) tracts, adjusted for total white matter hyperintensities volume: (A) Fractional anisotropy, (B) Mean diffusivity, (C) Orientation dispersion index, (D) Isotropic (free) water volume fraction, and (E) Intra-cellular volume fraction – a measure of neurite density. Red color represents positive association and blue color represents negative association. Only WM tracts reaching significance after Bonferroni correction are colored.

Supplemental Figure 4. Statistical significance of association between systolic blood pressure and white matter tracts diffusion metrics, adjusted for anti-hypertensive medication intake.



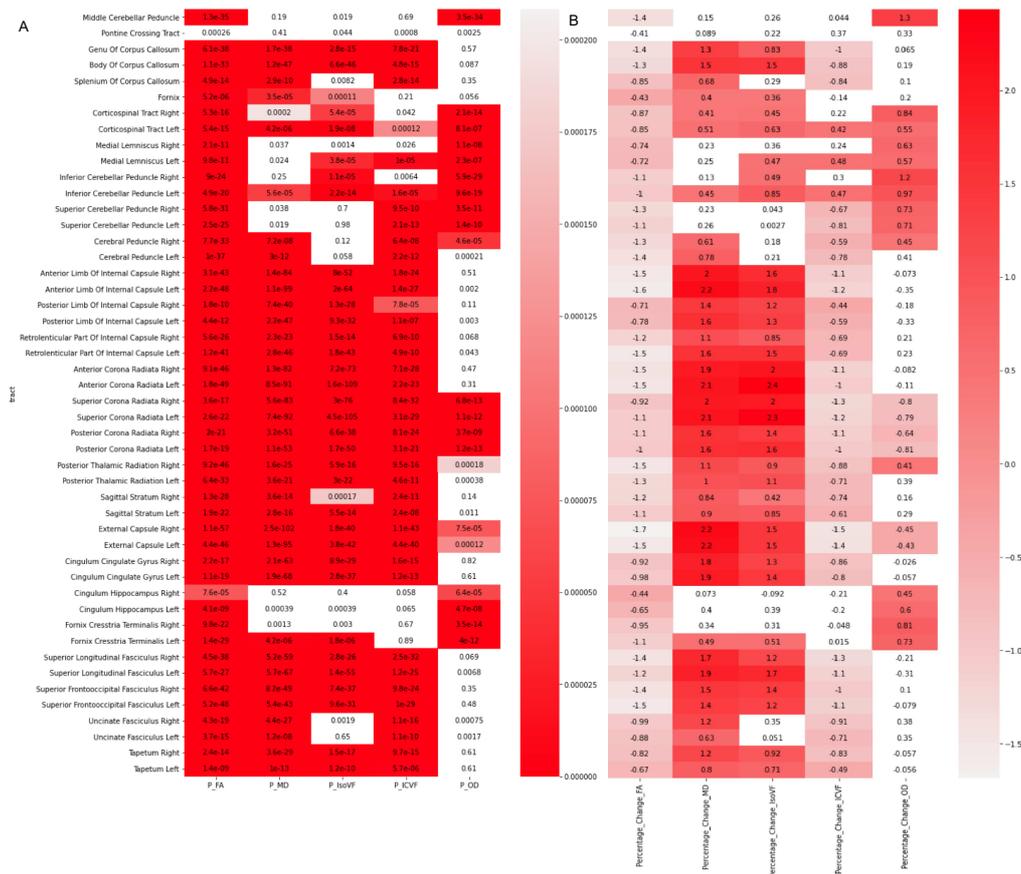
Supplemental Figure 4. Statistical significance from association analyses results between systolic blood pressure (SBP) and diffusion metrics across white matter tracts, adjusted for anti-hypertensive medication intake. The color bars represent p-values from multivariable regression models. Only p-values reaching significance after Bonferroni correction are colored.

Supplemental Figure 5. Topographic association of systolic blood pressure with white matter tracts diffusion metrics, adjusted for anti-hypertensive medication intake.



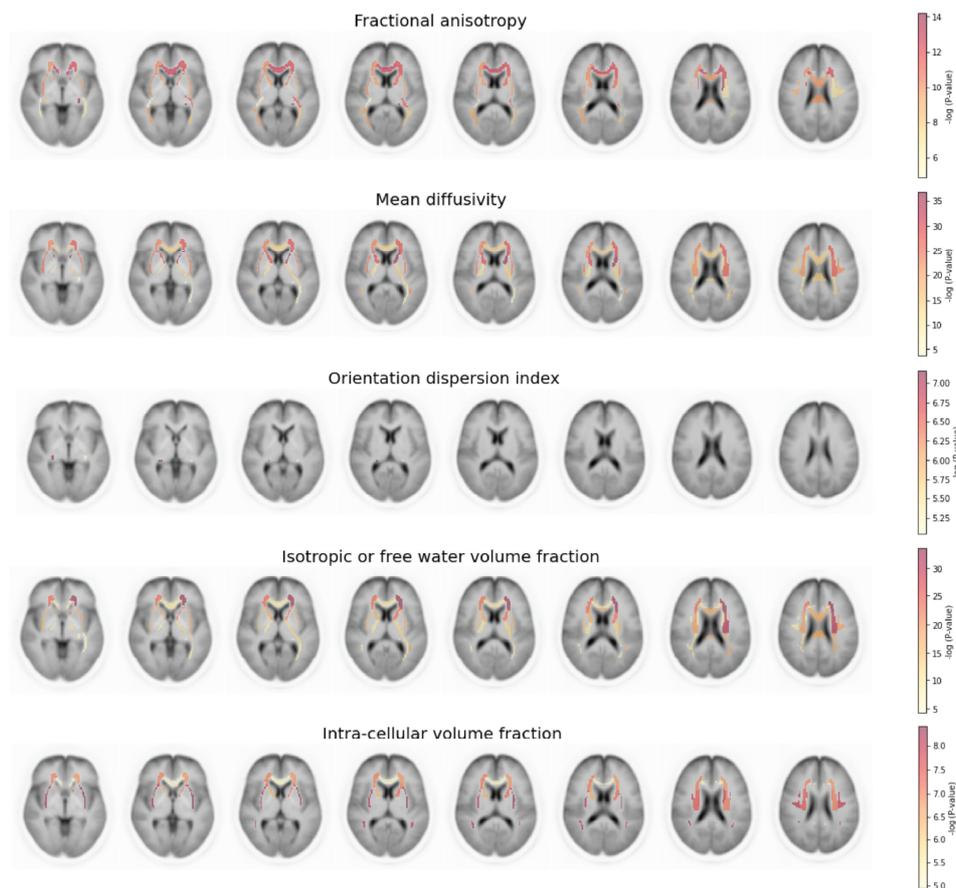
Supplemental Figure 5. Statistical significance from association analyses results between systolic blood pressure (SBP) and diffusion metrics across white matter (WM) tracts, adjusted for anti-hypertensive medication intake: (A) Fractional anisotropy, (B) Mean diffusivity, (C) Orientation dispersion index, (D) Isotropic (free) water volume fraction, and (E) Intra-cellular volume fraction – a measure of neurite density. The color bars represent $-\log_{10}$ p-values from multivariable regression models. Only WM tracts reaching significance after Bonferroni correction are colored.

Supplemental Figure 6. Statistical significance and effect size of association between systolic blood pressure and white matter tracts diffusion metrics, adjusted for educational level.



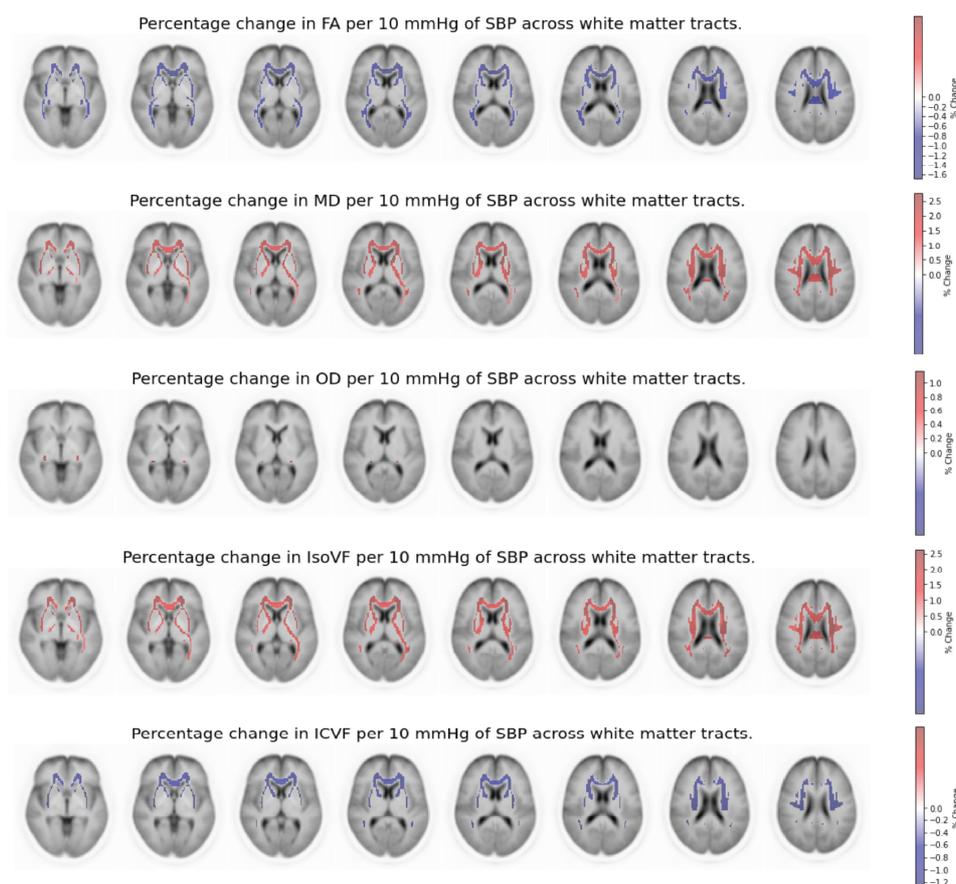
Supplemental Figure 6. (A) Statistical significance from association analyses results between systolic blood pressure (SBP) and diffusion metrics across white matter tracts, adjusted for educational level. Color bars represent p-values from multivariable regression models. Only p-values reaching significance after Bonferroni correction are colored. (B) Average percentage change in DTI metrics for each 10 mmHg increase in systolic blood pressure across white matter tracts, adjusted for educational level. The color bars represent the percentage change. Only values reaching significance after Bonferroni correction are colored.

Supplemental Figure 7. Topographic association of systolic blood pressure with white matter tracts diffusion metrics in the young age strata (minimum to 33rd percentile).



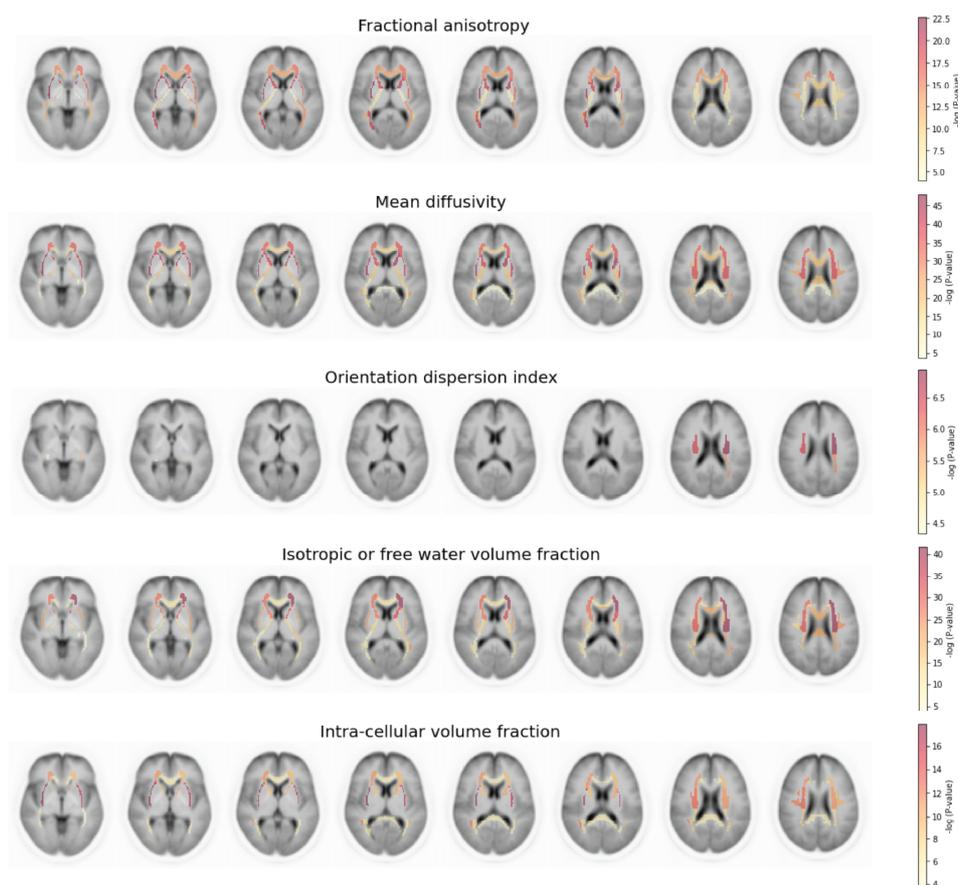
Supplemental Figure 7. Statistical significance from association analyses results between systolic blood pressure (SBP) and diffusion metrics across white matter (WM) tracts in the young age strata with a mean (standard deviation) age of 54.96 (3.42) years: (A) Fractional anisotropy, (B) Mean diffusivity, (C) Orientation dispersion index, (D) Isotropic (free) water volume fraction, and (E) Intra-cellular volume fraction – a measure of neurite density. The color bars represent $-\log_{10}$ p-values from multivariable regression models. Only WM tracts reaching significance after Bonferroni correction are colored.

Supplemental Figure 8. Percentage change in white matter tracts diffusion metrics per 10 mmHg increase in systolic blood pressure in the young age strata (minimum to 33rd percentile).



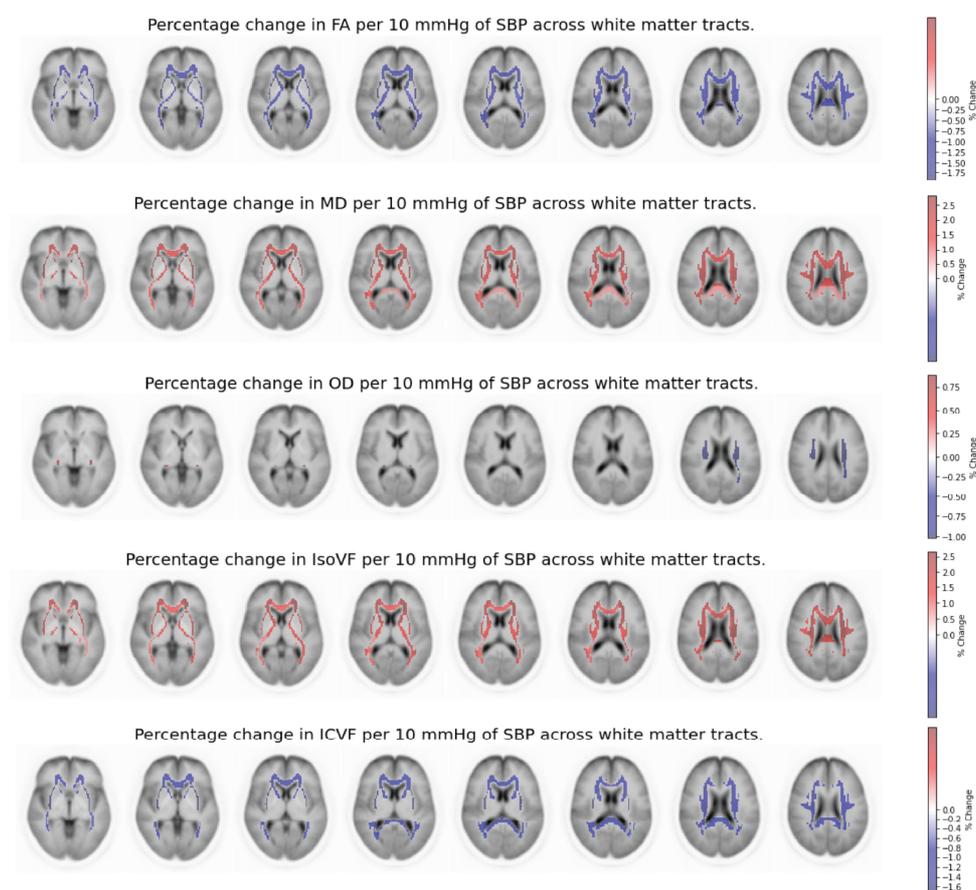
Supplemental Figure 8. Average percentage change in DTI metrics for each 10 mmHg increase in systolic blood pressure (SBP) across white matter (WM) tracts in the young age strata with a mean (standard deviation) age of 54.96 (3.42) years: (A) Fractional anisotropy, (B) Mean diffusivity, (C) Orientation dispersion index, (D) Isotropic (free) water volume fraction, and (E) Intra-cellular volume fraction – a measure of neurite density. Red color represents positive association and blue color represents negative association. Only WM tracts reaching significance after Bonferroni correction are colored.

Supplemental Figure 9. Topographic association of systolic blood pressure with white matter tracts diffusion metrics in the mid age strata (33rd to 67th percentile).



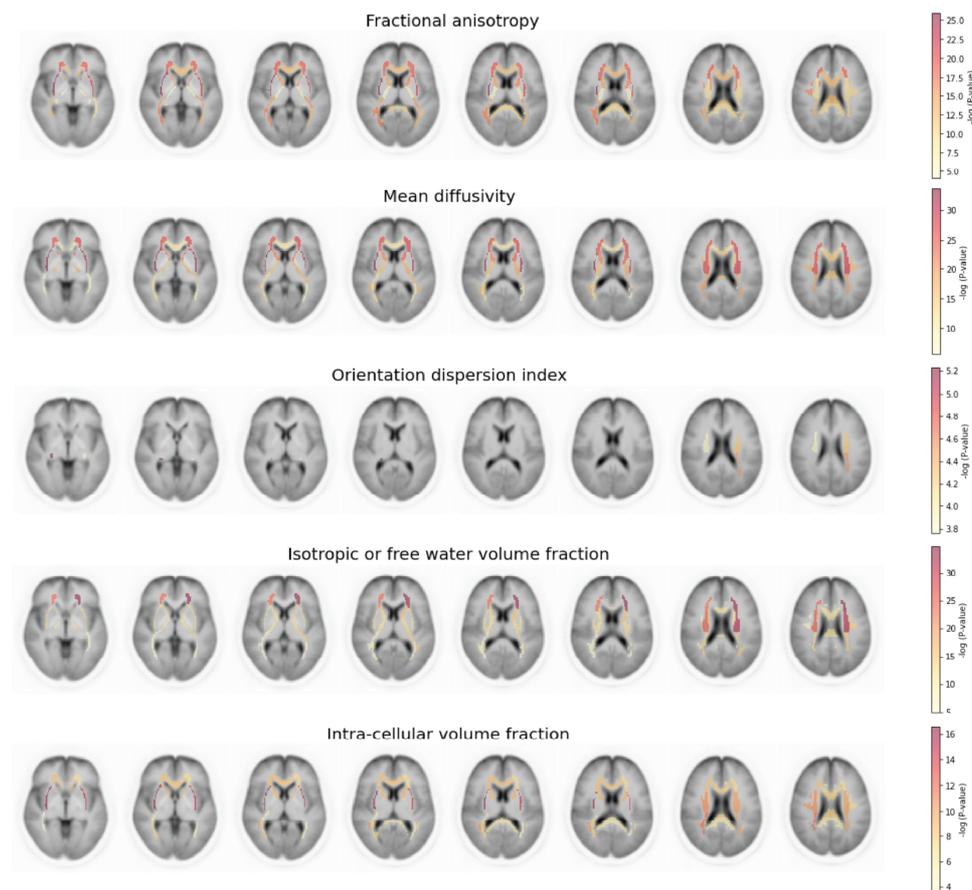
Supplemental Figure 9. Statistical significance from association analyses results between systolic blood pressure (SBP) and diffusion metrics across white matter (WM) tracts in the mid age strata with a mean (standard deviation) age of 64.26 (2.28) years: (A) Fractional anisotropy, (B) Mean diffusivity, (C) Orientation dispersion index, (D) Isotropic (free) water volume fraction, and (E) Intra-cellular volume fraction – a measure of neurite density. The color bars represent $-\log_{10}$ p-values from multivariable regression models. Only WM tracts reaching significance after Bonferroni correction are colored.

Supplemental Figure 10. Percentage change in white matter tracts diffusion metrics per 10 mmHg increase in systolic blood pressure in the mid age strata (33rd to 67th percentile).



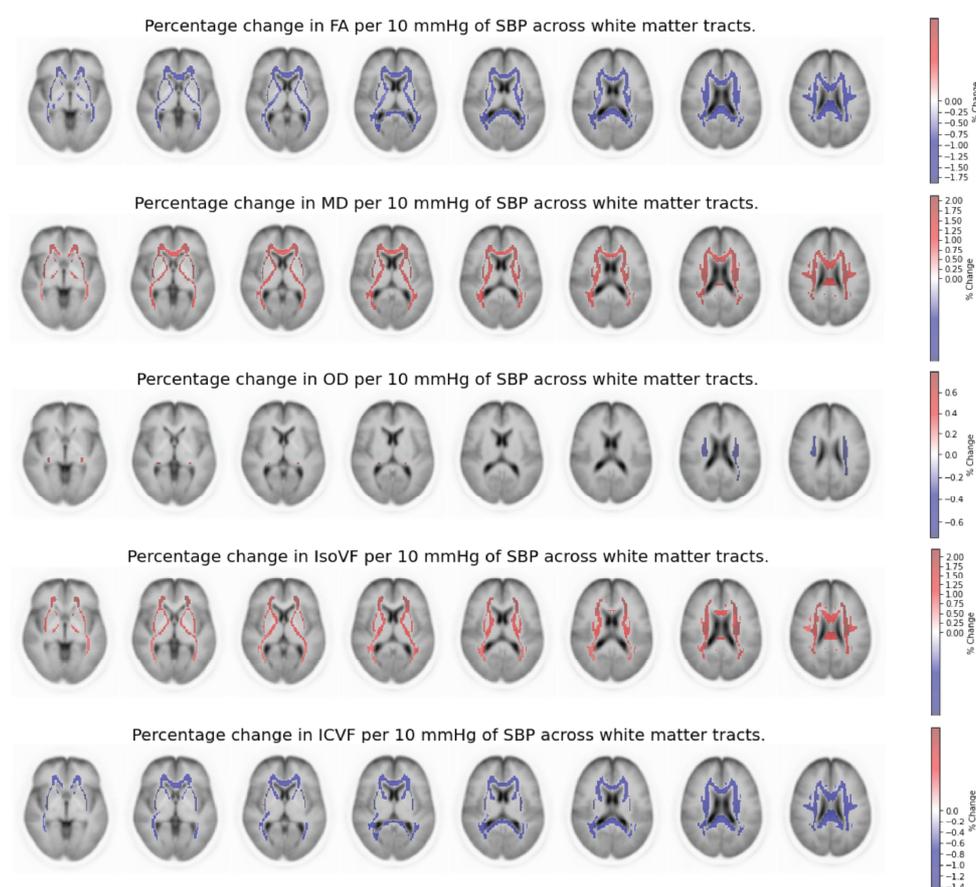
Supplemental Figure 10. Average percentage change in DTI metrics for each 10 mmHg increase in systolic blood pressure (SBP) across white matter (WM) tracts in the mid age strata with a mean (standard deviation) age of 64.26 (2.28) years: (A) Fractional anisotropy, (B) Mean diffusivity, (C) Orientation dispersion index, (D) Isotropic (free) water volume fraction, and (E) Intra-cellular volume fraction – a measure of neurite density. Red color represents positive association and blue color represents negative association. Only WM tracts reaching significance after Bonferroni correction are colored.

Supplemental Figure 11. Topographic association of systolic blood pressure with white matter tracts diffusion metrics in the old age strata (67th percentile to max).



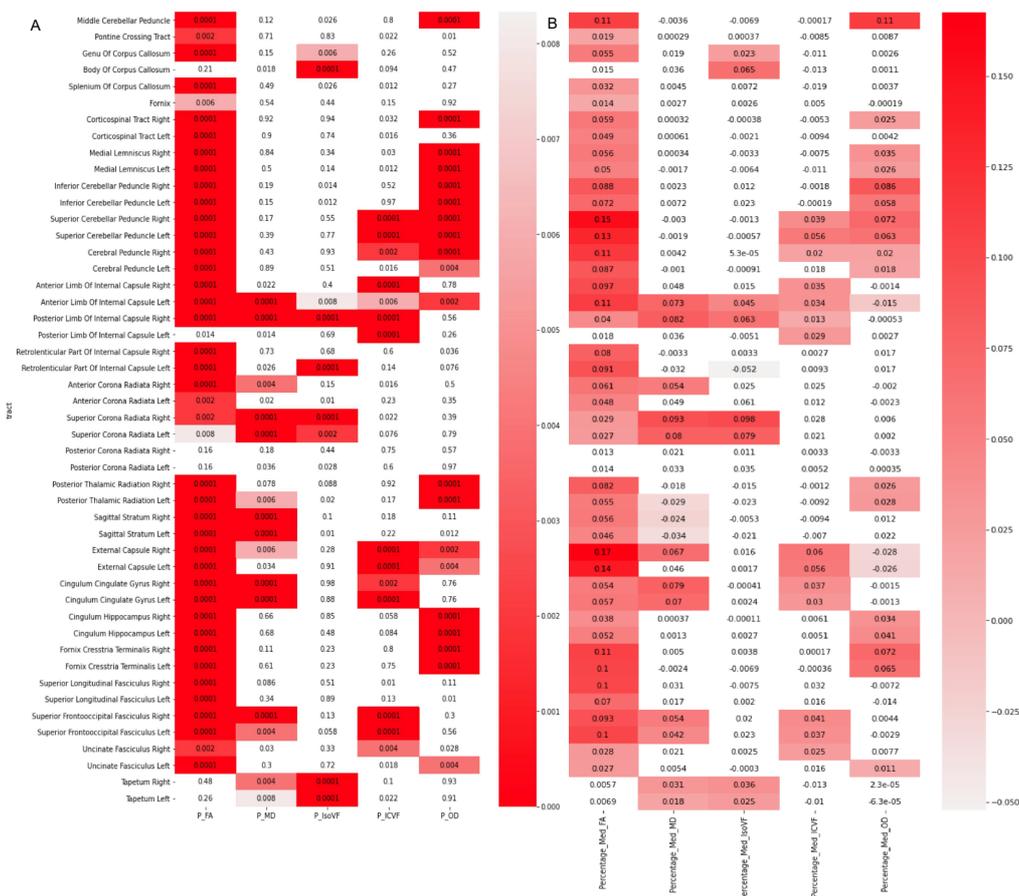
Supplemental Figure 11. Statistical significance from association analyses results between systolic blood pressure (SBP) and diffusion metrics across white matter (WM) tracts in the old age strata with a mean (standard deviation) age of 72.29 (3.05) years: (A) Fractional anisotropy, (B) Mean diffusivity, (C) Orientation dispersion index, (D) Isotropic (free) water volume fraction, and (E) Intra-cellular volume fraction – a measure of neurite density. The color bars represent $-\log_{10}$ p-values from multivariable regression models. Only WM tracts reaching significance after Bonferroni correction are colored.

Supplemental Figure 12. Percentage change in white matter tracts diffusion metrics per 10 mmHg increase in systolic blood pressure in the old age strata (67th percentile to max).



Supplemental Figure 12. Average percentage change in DTI metrics for each 10 mmHg increase in systolic blood pressure (SBP) across white matter (WM) tracts in the old age strata with a mean (standard deviation) age of 72.29 (3.05) years: (A) Fractional anisotropy, (B) Mean diffusivity, (C) Orientation dispersion index, (D) Isotropic (free) water volume fraction, and (E) Intra-cellular volume fraction – a measure of neurite density. Red color represents positive association and blue color represents negative association. Only WM tracts reaching significance after Bonferroni correction are colored.

Supplemental Figure 13. Statistical significance and effect size of mediation analysis, adjusted for educational level.



Supplemental Figure 13. (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, adjusted for educational level. Color 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. Color bars represent the average mediated effects proportion. Only average mediated effects associated with p-values reaching significance after Bonferroni correction are highlighted.