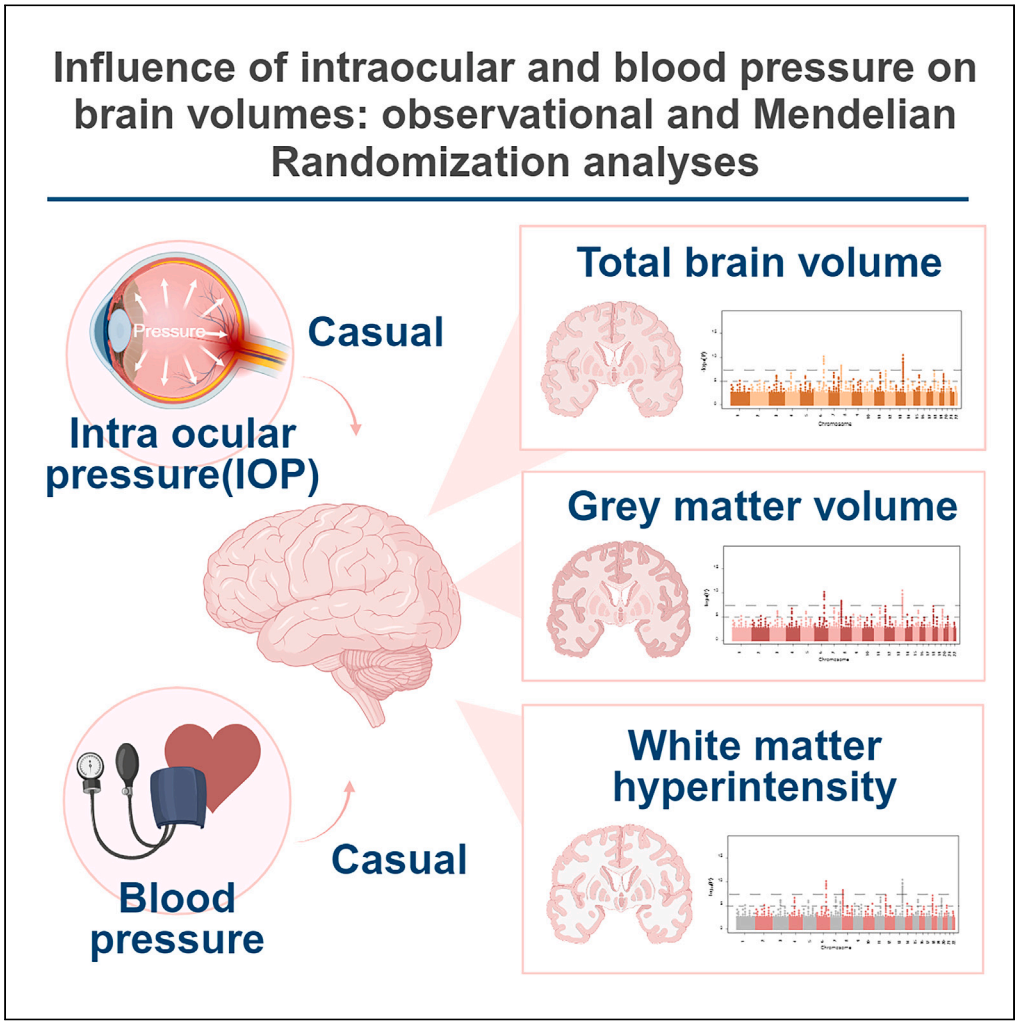
iScience

CellPress
OPEN ACCESS

Article

Influence of intraocular and blood pressure on brain volumes: Observational and Mendelian randomization analyses



Xianwen Shang, Yu Huang, Susan Zhu, ..., Honghua Yu, Xiaohong Yang, Mingguang He

huangyu4244@gdph.org.cn (Y.H.)
yuhonghua@gdph.org.cn (H.Y.)
syyangxh@scut.edu.cn (X.Y.)
mingguang_he@yahoo.com (M.H.)

Highlights

Higher IOP is linked to reduced gray matter volume

Increased DBP is associated with a larger WMH load

Younger individuals show stronger associations between IOP and brain volumes

Lowering IOP in young individuals without hypertension may prevent brain volume loss

Shang et al., iScience 27, 110817
November 15, 2024
https://doi.org/10.1016/j.isci.2024.110817

iScience

CellPress
OPEN ACCESS

Article

Influence of intraocular and blood pressure on brain volumes: Observational and Mendelian randomization analyses

Xianwen Shang,[1,2,3,4,9,11] Yu Huang,[1,2,11,12,*] Susan Zhu,[5] Zhuoting Zhu,[1,2,3] Xueli Zhang,[1] Wei Wang,[6] Xiayin Zhang,[1,2] Jing Liu,[1] Jiahao Liu,[7] Shulin Tang,[1] Zongyuan Ge,[8] Yijun Hu,[1] Honghua Yu,[1,*] Xiaohong Yang,[1,*] and Mingguang He[1,3,4,6,9,10,*]

SUMMARY

Intraocular pressure (IOP) is closely correlated with blood pressure (BP), and while BP has been linked to brain volumes, the effect of IOP on brain volumes remains unclear. This study analyzed participants from the UK Biobank with MRI-measured brain volumes. Observational analyses included 8,634 participants for IOP and 36,069 for BP, followed by Mendelian randomization (MR) analyses of 37,410 participants. Observational analyses revealed that each 10-mmHg increase in diastolic BP was linked to a 0.13 mL larger white matter hyperintensity (WMH) after adjusting for covariates. Associations between IOP and brain volumes were more pronounced in younger individuals or those without hypertension. MR analyses confirmed significant relationships between diastolic BP and WMH, and each 5-mmHg increase in IOP reduced gray matter volumes by 3.24 mL. The study suggests that targeting IOP and BP could help prevent brain volume reduction.

INTRODUCTION

Neurological diseases are the leading cause of disability and the second leading cause of death worldwide.[1] Brain atrophy is a key presentation of many progressive neurological diseases including Alzheimer's disease,[2,3] and multiple sclerosis.[4] Importantly, brain volume can be clinically used to measure the degree of neurodegeneration, thereby determining the prognosis and appropriate treatment.[2,5,6] However, evidence has shown that conventional factors including diabetes, hypercholesterolaemia, and obesity appeared to explain a small amount of additional variance beyond covariates for brain atrophy (age and sex).7,8 Therefore, it is important to identify new determinants for brain atrophy.

Systemic hypertension has been linked to greater brain atrophy in many previous observational studies.[7–10] Although there is a high correlation between systemic blood pressure (BP) especially systolic BP (SBP), and intraocular pressure (IOP),[11–13] the association between IOP and brain atrophy has been investigated in only a few studies with inconsistent results.[14,15] Traditional observational studies can be used to investigate the association between biomarkers and health conditions; however, they are prone to bias and cannot be used to refer to causal relationships.[16] Mendelian randomization (MR) analysis overcomes these problems by using genetic variants as instrumental variables (IVs) to avoid confounding bias and measuring their effects on outcome,[16] which can be used to infer causal relationships. However, no previous MR analysis has examined potential causal relationships between BP, IOP, and brain volumes.

Using the UK biobank, we aimed to investigate the relationships between systemic BP, IOP, and brain volume. Importantly, both MR and traditional observational analyses were performed, providing genetic and phenotypic evidence for any associations.

[1]Guangdong Eye Institute, Department of Ophthalmology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou 510080, China
[2]Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China
[3]Centre for Eye Research Australia, Melbourne, VIC 3002, Australia
[4]School of Optometry, The Hong Kong Polytechnic University, Kowloon, Hong Kong, China
[5]Austin Hospital, University of Melbourne, Melbourne, VIC 3084, Australia
[6]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou 510060, China
[7]Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC 3010, Australia
[8]Monash e-Research Center, Faculty of Engineering, Airdoc Research, Nvidia AI Technology Research Center, Monash University, Melbourne, VIC 3800, Australia
[9]Research Centre for SHARP Vision (RCSV), The Hong Kong Polytechnic University, Kowloon, Hong Kong, China
[10]Centre for Eye and Vision Research (CEVR), 17W Hong Kong Science Park, Hong Kong, China
[11]These authors contributed equally
[12]Lead contact
*Correspondence: huangyu4244@gdph.org.cn (Y.H.), yuhonghua@gdph.org.cn (H.Y.), syyangxh@scut.edu.cn (X.Y.), mingguang_he@yahoo.com (M.H.)
https://doi.org/10.1016/j.isci.2024.110817

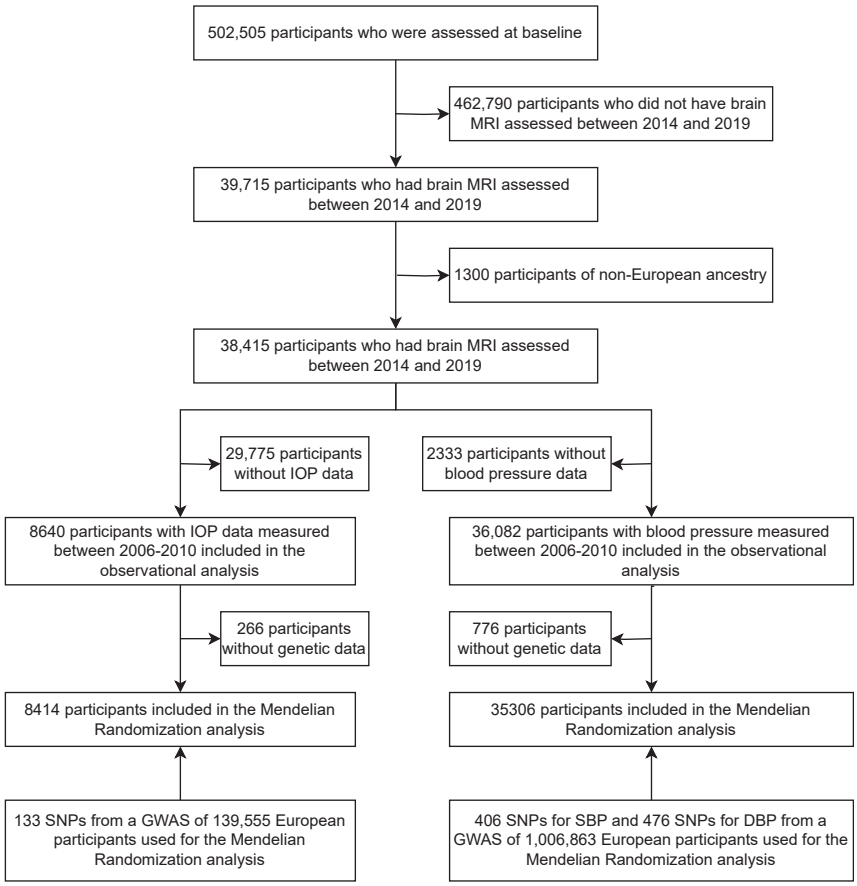


Figure 1. Flowchart for population selection from the UK Biobank IOP = intraocular pressure; MRI = magnetic resonance imaging

RESULTS

Baseline characteristics

Of the 502,505 participants with baseline data, individuals who did not have MRI data (n = 462,809), or those of non-European ancestry (n = 1294) were excluded from the analysis (Figure 1). After further excluding those without IOP data (n = 29,768), 8634 adults (52.5% females) aged 40–70 (mean ± SD: 55.8 ± 7.4) years at baseline were included in the analysis for the association between IOP and brain volumes. They were aged 45–80 (63.3 ± 7.5) years when MRI data were collected 7.7 (interquartile range: 6.3–8.9) years later. After excluding those without BP data (n = 2,333), 36,069 adults (53.0% females) aged 40–70 (mean ± SD: 55.0 ± 7.4) years at baseline were included in the analysis for the association between BP and brain volumes. They were aged 45–81 (63.7 ± 7.5) years when MRI data were collected 8.9 (interquartile range: 7.4 to 10.0) years later.

Individuals with higher IOP were more likely to have lower income and to be older. Higher IOP was associated with a higher prevalence of systemic hypertension, glaucoma, and higher levels of BMI, LDL-C, and HbA1c (Table 1). Individuals with higher DBP were more likely to be older, males, physically inactive, non-current smokers, and glaucoma patients (Table S12). Individuals with higher SBP were more likely to be older, males, physically active, non-current smokers, and glaucoma patients (Table S13).

Phenotypic association between intraocular pressure and brain volumes

The IOP quintiles were categorized as follows: Quintile 1 (<12.5 mmHg), Quintile 2 (12.5–14.3 mmHg), Quintile 3 (14.4–16.0 mmHg), Quintile 4 (16.1–18.2 mmHg), and Quintile 5 (>18.2 mmHg). Increased IOP was associated with smaller volumes of the total brain (β (95% CI) for Quintile 5 versus Quintile 1: −19.54 mL, −24.36 to −14.72), gray matter (−12.02 mL, −15.19 to −8.85), white matter (−7.52 mL, −10.23 to −4.81), hippocampus (−29.58 μL, −58.69 to −0.48), and larger ventricular cerebrospinal fluid volume (4.61 mL, 3.29 to 5.94). These associations for total brain (−4.82 mL, −9.03 to −0.61), white matter (−3.20 mL, −5.92 to −0.48), and ventricular cerebrospinal fluid (1.61 mL, 0.43 to 2.80) remained significant after adjustment for geographic factors, lifestyle factors, BMI, lipids, BP, self-reported hypertension, and the use of medication for hypertension/glaucoma. In the multivariable-adjusted analysis, increased IOP was associated with smaller volumes of the total brain (β (95% CI) for each 5-mmHg increment: −3.24 mL, −5.05 to −1.44), gray matter (−1.10 mL, −2.17 to −0.03), and white matter (−2.14 mL, −3.32 to −0.97), and larger ventricular cerebrospinal fluid volume (0.75 mL, 0.23 to 1.28) (Table 2).

Table 1. Baseline characteristics of participants by quintiles of intraocular pressure

Variables	Intraocular pressure					
	Quintile 1 (*n* = 1731)	Quintile 2 (*n* = 1720)	Quintile 3 (*n* = 1726)	Quintile 4 (*n* = 1730)	Quintile 5 (*n* = 1727)	*P*-value[a]
Range (mmHg)	<12.5	12.5–14.3	14.4–16.0	16.1–18.2	>18.2	
Age (years)	54.5 ± 7.6	55.3 ± 7.5	55.9 ± 7.3	56.4 ± 7.3	56.9 ± 7.2	<0.0001
Gender						0.21
Female	898 (51.9)	922 (53.6)	931 (53.9)	929 (53.7)	854 (49.4)	
Male	833 (48.1)	798 (46.4)	795 (46.1)	801 (46.3)	873 (50.6)	
APOE4						0.94
No	1301 (75.2)	1268 (73.7)	1283 (74.3)	1306 (75.5)	1278 (74.0)	
Yes	387 (22.4)	396 (23.0)	407 (23.6)	390 (22.5)	405 (23.5)	
Missing	43 (2.5)	56 (3.3)	36 (2.1)	34 (2.0)	44 (2.5)	
Education						0.90
0–5 years	84 (4.9)	99 (5.8)	84 (4.9)	98 (5.7)	108 (6.3)	
6–12 years	835 (48.2)	800 (46.5)	834 (48.3)	832 (48.1)	782 (45.3)	
≥13 years	808 (46.7)	817 (47.5)	802 (46.5)	792 (45.8)	828 (47.9)	
Missing	4 (0.2)	4 (0.2)	6 (0.3)	8 (0.5)	9 (0.5)	
Household income (pounds)						<0.0001
<18,000	174 (10.1)	168 (9.8)	169 (9.8)	182 (10.5)	188 (10.9)	
18,000–30,999	328 (18.9)	332 (19.3)	337 (19.5)	348 (20.1)	392 (22.7)	
31,000–51,999	473 (27.3)	482 (28.0)	458 (26.5)	488 (28.2)	475 (27.5)	
52,000–100,000	485 (28.0)	464 (27.0)	491 (28.4)	433 (25.0)	424 (24.6)	
>100,000	143 (8.3)	141 (8.2)	135 (7.8)	123 (7.1)	110 (6.4)	
Unknown	27 (1.6)	27 (1.6)	38 (2.2)	33 (1.9)	37 (2.1)	
Not answered	101 (5.8)	106 (6.2)	98 (5.7)	123 (7.1)	101 (5.8)	
Physical activity (MET-minutes/week)	2596 ± 2476	2593 ± 2307	2468 ± 2168	2572 ± 2256	2489 ± 2182	0.18
Alcohol consumption						0.20
Never	35 (2.0)	38 (2.2)	30 (1.7)	33 (1.9)	38 (2.2)	
Previous	49 (2.8)	33 (1.9)	34 (2.0)	36 (2.1)	30 (1.7)	
Current	1647 (95.1)	1649 (95.9)	1661 (96.2)	1661 (96.0)	1659 (96.1)	
Missing			1 (0.1)			
Smoking						0.93
Never	1067 (61.6)	1053 (61.2)	1049 (60.8)	1044 (60.3)	1053 (61.0)	
Former	558 (32.2)	565 (32.8)	570 (33.0)	585 (33.8)	579 (33.5)	
Current	105 (6.1)	99 (5.8)	103 (6.0)	97 (5.6)	89 (5.2)	
Missing	1 (0.1)	3 (0.2)	4 (0.2)	4 (0.2)	6 (0.3)	
Sleep duration (hours)	7.11 ± 0.92	7.15 ± 0.92	7.18 ± 0.96	7.19 ± 0.95	7.23 ± 0.99	0.0001
BMI (kg/m^2)	26.36 ± 4.06	26.46 ± 4.11	26.74 ± 4.33	26.80 ± 3.92	27.07 ± 4.37	<0.0001
Total cholesterol (mmol/L)	5.69 ± 1.03	5.76 ± 1.04	5.73 ± 1.08	5.80 ± 1.08	5.79 ± 1.04	0.0032
HDL-C (mmol/L)	1.48 ± 0.35	1.49 ± 0.36	1.49 ± 0.36	1.50 ± 0.36	1.49 ± 0.36	0.13
LDL-C (mmol/L)	3.54 ± 0.79	3.59 ± 0.78	3.57 ± 0.81	3.61 ± 0.81	3.61 ± 0.81	0.0083
Triglycerides (mmol/L)	1.62 ± 0.89	1.67 ± 0.97	1.64 ± 0.90	1.69 ± 0.92	1.67 ± 0.92	0.0733
HbA1c (mmol/mol)	34.66 ± 4.33	35.01 ± 4.54	35.00 ± 4.41	35.47 ± 5.48	35.66 ± 5.98	<0.0001
Hypertension	279 (16.1)	308 (17.9)	367 (21.3)	371 (21.4)	393 (22.8)	<0.0001
Heart disease	34 (2.0)	27 (1.6)	43 (2.5)	43 (2.5)	42 (2.4)	0.0972
Depression	103 (6.0)	95 (5.5)	85 (4.9)	76 (4.4)	75 (4.3)	0.0091

(*Continued on next page*)

Table 1. *Continued*

Variables	Intraocular pressure					
	Quintile 1 (*n* = 1731)	Quintile 2 (*n* = 1720)	Quintile 3 (*n* = 1726)	Quintile 4 (*n* = 1730)	Quintile 5 (*n* = 1727)	*P*-value[a]
Glaucoma	8 (0.5)	8 (0.5)	17 (1.0)	25 (1.4)	49 (2.8)	<0.0001
Medication for glaucoma	4 (0.2)		4 (0.2)	5 (0.3)	9 (0.5)	0.0277

Data are mean ± standard deviations, or N (%). BMI, body mass index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent.

[a]ANOVA was used to test the difference of continuous variables across quintiles of IOP and Chi-square for categorical variables.

Phenotypic association between systemic blood pressure and brain volumes

Increased SBP was associated with smaller volumes of total brain, gray matter, and white matter, higher WMH load, and larger ventricular cerebrospinal fluid volume. The associations for total brain and gray matter volumes were attenuated to be non-significant after adjustment for age and gender. In Model 3, βs (95% CIs) for hippocampal volume and WMH load associated with SBP (Quintile 5 versus Quintile 1) were −22.24 μL (−37.13 to −7.35) and 0.29 mL (0.25–0.33), respectively. These associations were attenuated to be non-significant after adjustment for medication use for IOP, glaucoma, and the use of medication for hypertension/glaucoma (Table 3). Increased DBP was associated with higher WMH load (β (95% CI) for each 10-mmHg increment: 0.13 mL (0.05–0.21)) but not volumes of other regions after adjustment for IOP, glaucoma, the use of medication for hypertension/glaucoma and other covariates (Table 4).

Moderation analysis

Significant interactions were observed between age and IOP for volumes of total brain and WMH. The association between IOP and total brain volume was more pronounced in younger individuals (β (95% CI): −7.51 mL, −10.08 to −4.94) compared to older individuals (−2.51 mL, −5.23 to 0.22) (*P*-value for interaction = 0.0090). The association between IOP and WMH load was significant in younger individuals (0.17 mL, 0.04 to 0.30), but not in older individuals (−0.07 mL (−0.22, 0.08)). The association between IOP and total brain volume was significant in individuals without systemic hypertension (β (95% CI): −10.11 mL, −12.47 to −7.74), but not in those with (−2.95 mL, −7.64 to 1.75). Similarly, the association between IOP and gray matter volume was more pronounced in those without systemic hypertension (−6.28 mL, −7.81 to −4.74) than in those with (−1.05 mL, −4.21 to 2.12). In individuals without systemic hypertension, the association between IOP and ventricular cerebrospinal fluid was also more pronounced (Figure 2).

The association between DBP and volumes of total brain, gray matter, WMH, and ventricular cerebrospinal fluid was more pronounced in older individuals, women, and those with low levels of education. β (95% CI) for WMH volume associated with DBP was 0.19 mL (0.17–0.21), 0.18 mL (0.16–0.20), and 0.10 mL (0.05–0.15) for individuals with low, moderate, and high education (Figure S2). Similar results were seen for SBP (Figure S3).

Mendelian randomization analysis

All MR analytic methods demonstrated a significant relationship between DBP and WMH. The β (95% CI) for WMH associated with each 10-mmHg increment of DBP was 0.019 mL (0.013–0.026) for IVW, 0.022 (0.01–0.033) for MR-Egger, 0.027 mL (0.018–0.036) for weighted median, and 0.018 mL (0.012–0.024) for MR-PRESSO. The IVW (β (95% CI): −1.37 mL, −2.50 to −0.24) and MR-PRESSO (−1.22 mL, −2.30, −0.14) methods showed a significant association between IOP and total brain volume, while other MR methods did not yield significant results. Furthermore, the β (95% CI) for gray matter volume associated with each 5-mmHg increment of IOP varied across MR methods were −3.42 mL (−5.39 to −1.45) for IVW (*P*-value = 0.0010), −3.21 mL (−6.54 to 0.12) for MR-Egger (*P*-value = 0.0590), −2.55 mL (−5.12 to 0.02) for weighted median (*P*-value = 0.0510), and −2.98 mL (−4.88 to −1.09) for MR-PRESSO (*P*-value = 0.00271). Additionally, increased IOP was significantly associated with larger ventricular cerebrospinal fluid volume in the MR analysis using IVW and MR-PRESSO. After considering the sample overlap issue, the relationship between IOP and gray matter as well as ventricular cerebrospinal fluid volume remained similar. No other significant relationships were observed (Figure 3).

Genetic risk score and brain volumes

Higher GRS for IOP was associated with smaller total brain and gray matter volumes, as well as a larger ventricular cerebrospinal fluid volume. In Model 4, βs (95% CIs) for total brain, gray matter, and ventricular cerebrospinal fluid volumes (mL) associated with GRS for IOP (Quintile 5 versus Quintile 1) were −3.09 mL (−5.02 to −1.17), −2.13 mL (−3.27 to −0.98), and 1.31 mL (0.75–1.86), respectively (Table S14). Higher GRS for DBP was associated with higher WMH load (β (95% CI) for Quintile 5 versus Quintile 1: 0.08 mL (0.05–0.12), Table S15).

Sensitivity analysis

The inverse probability weighting analysis showed that increased IOP was independently associated with smaller volumes of total brain (β (95% CI) for each 5-mmHg increment of IOP: −2.69 mL, −4.49 to −0.89) and gray matter (−1.24 mL, −2.31 to −0.17), as well as a larger

Table 2. Association between intraocular pressure and brain volumes

Brain volume	Intraocular pressure (mmHg) Quintile 1, <12.5 (*n* = 1731)	Quintile 2, 12.5–14.3 (*n* = 1720)	Quintile 3, 14.4–16.0 (*n* = 1726)	Quintile 4, 16.1–18.2 (*n* = 1730)	Quintile 5, >18.2 (*n* = 1727)	*P*-value for trend	Each 5-mmHg increment[a]
Total brain							
Volume (mL)	1505 ± 74	1501 ± 73	1496 ± 72	1490 ± 72	1486 ± 71	<0.0001	
β (95% CI), Model 1[b]	Reference	−4.77 (−9.60, 0.06)	−8.80 (−13.62, −3.98)	−14.84 (−19.66, −10.02)	−19.54 (−24.36, −14.72)	<0.0001	−9.50 (−11.63, −7.36)
β (95% CI), Model 2	Reference	−1.26 (−5.27, 2.76)	−2.02 (−6.03, 2.00)	−5.68 (−9.70, −1.66)	−6.98 (−11.01, −2.95)	0.0001	−3.57 (−5.35, −1.79)
β (95% CI), Model 3	Reference	−0.58 (−4.74, 3.59)	−1.68 (−5.83, 2.47)	−4.09 (−8.27, 0.09)	−5.19 (−9.39, −0.98)	0.0039	−3.11 (−4.89, −1.33)
β (95% CI), Model 4	Reference	−1.21 (−5.21, 2.79)	−1.72 (−5.73, 2.30)	−5.71 (−9.75, −1.68)	−6.60 (−10.67, −2.54)	0.0001	−3.43 (−5.23, −1.63)
Gray matter							
Volume (mL)	799 ± 48	796 ± 47	793 ± 48	790 ± 47	787 ± 48	<0.0001	
β (95% CI), Model 1	Reference	−2.45 (−5.62, 0.72)	−5.33 (−8.51, −2.16)	−8.13 (−11.30, −4.97)	−12.02 (−15.19, −8.85)	<0.0001	−5.93 (−7.33, −4.53)
β (95% CI), Model 2	Reference	−0.24 (−2.64, 2.16)	−0.89 (−3.29, 1.51)	−1.99 (−4.39, 0.41)	−2.87 (−5.28, −0.47)	0.0064	−1.55 (−2.62, −0.49)
β (95% CI), Model 3	Reference	0.13 (−2.34, 2.60)	−0.51 (−2.98, 1.95)	−0.93 (−3.41, 1.55)	−1.83 (−4.33, 0.66)	0.0981	−1.21 (−2.27, −0.16)
β (95% CI), Model 4	Reference	−0.09 (−2.46, 2.29)	−0.24 (−2.63, 2.14)	−1.55 (−3.94, 0.85)	−2.04 (−4.45, 0.38)	0.0452	−1.18 (−2.25, −0.11)
White matter							
Volume (mL)	707 ± 41	704 ± 42	703 ± 401	700 ± 40	699 ± 40	<0.0001	
β (95% CI), Model 1	Reference	−2.32 (−5.03, 0.39)	−3.46 (−6.17, −0.76)	−6.71 (−9.41, −4.00)	−7.52 (−10.23, −4.81)	<0.0001	−3.56 (−4.76, −2.37)
β (95% CI), Model 2	Reference	−1.01 (−3.60, 1.58)	−1.13 (−3.72, 1.46)	−3.69 (−6.28, −1.10)	−4.11 (−6.70, −1.51)	0.0002	−2.02 (−3.17, −0.87)
β (95% CI), Model 3	Reference	−0.70 (−3.40, 1.99)	−1.16 (−3.85, 1.52)	−3.17 (−5.87, −0.46)	−3.35 (−6.07, −0.63)	0.0032	−1.90 (−3.05, −0.74)
β (95% CI), Model 4	Reference	−1.13 (−3.72, 1.47)	−1.47 (−4.08, 1.13)	−4.17 (−6.78, −1.55)	−4.57 (−7.20, −1.93)	0.0001	−2.25 (−3.41, −1.08)
Hippocampus							
Volume (μL)	3877 ± 435	3872 ± 443	3857 ± 438	3841 ± 431	3847 ± 437	0.00605	
β (95% CI), Model 1	Reference	−5.91 (−35.04, 23.23)	−21.26 (−50.37, 7.85)	−35.97 (−65.06, −6.88)	−29.58 (−58.69, −0.48)	<0.0001	−15.74 (−28.61, −2.88)
β (95% CI), Model 2	Reference	10.50 (−16.57, 37.56)	6.43 (−20.64, 33.51)	−1.00 (−28.09, 26.10)	3.84 (−23.32, 30.99)	0.90	−1.26 (−13.26, 10.75)
β (95% CI), Model 3	Reference	8.34 (−19.74, 36.43)	3.53 (−24.43, 31.49)	2.89 (−25.28, 31.06)	7.79 (−20.54, 36.13)	0.75	0.39 (−11.61, 12.39)
β (95% CI), Model 4	Reference	9.99 (−17.02, 37.01)	7.46 (−19.65, 34.57)	0.42 (−26.82, 27.66)	8.58 (−18.88, 36.03)	<0.0001	0.63 (−11.53, 12.78)
White matter hyperintensity							
Volume (mL)	1.14 ± 1.08	0.91 ± 1.17	1.09 ± 0.97	1.06 ± 0.99	1.30 ± 1.08	0.10511	
β (95% CI), Model 1	Reference	−0.23 (−0.49, 0.02)	−0.05 (−0.32, 0.23)	−0.09 (−0.34, 0.17)	0.16 (−0.10, 0.41)	0.11	0.08 (−0.03, 0.18)
β (95% CI), Model 2	Reference	−0.20 (−0.43, 0.02)	−0.11 (−0.36, 0.13)	−0.16 (−0.39, 0.06)	0.02 (−0.20, 0.24)	0.73	0.02 (−0.07, 0.16)
β (95% CI), Model 3	Reference	−0.20 (−0.44, 0.04)	−0.05 (−0.31, 0.21)	−0.16 (−0.41, 0.08)	0.01 (−0.22, 0.25)	0.74	0.03 (−0.06, 0.12)
β (95% CI), Model 4	Reference	−0.18 (−0.40, 0.05)	−0.08 (−0.32, 0.16)	−0.21 (−0.44, 0.02)	0.04 (−0.19, 0.26)	0.82	0.01 (−0.08, 0.11)

(*Continued on next page*)

Table 2. *Continued*

Brain volume	Intraocular pressure (mmHg) Quintile 1, <12.5 (*n* = 1731)	Quintile 2, 12.5–14.3 (*n* = 1720)	Quintile 3, 14.4–16.0 (*n* = 1726)	Quintile 4, 16.1–18.2 (*n* = 1730)	Quintile 5, >18.2 (*n* = 1727)	*P*-value for trend	Each 5-mmHg increment[a]
Ventricular cerebrospinal fluid							
Volume (mL)	44.0 ± 19.0	45.6 ± 20.0	45.9 ± 18.8	47.8 ± 21.2	48.6 ± 20.4	<0.0001	
β (95% CI), Model 1	Reference	1.61 (0.29, 2.94)	1.93 (0.61, 3.26)	3.83 (2.50, 5.16)	4.61 (3.29, 5.94)	<0.0001	2.20 (1.61, 2.79)
β (95% CI), Model 2	Reference	0.92 (−0.25, 2.08)	0.52 (−0.65, 1.68)	1.91 (0.74, 3.08)	1.77 (0.60, 2.94)	0.0007	0.84 (0.32, 1.35)
β (95% CI), Model 3	Reference	0.88 (−0.28, 2.05)	0.48 (−0.69, 1.64)	1.85 (0.69, 3.02)	1.66 (0.49, 2.82)	0.0014	0.77 (0.25, 1.29)
β (95% CI), Model 4	Reference	0.91 (−0.26, 2.07)	0.44 (−0.73, 1.61)	1.85 (0.68, 3.03)	1.61 (0.43, 2.80)	0.0021	0.75 (0.23, 1.28)

[a]General linear regression models were used to estimate the association between intraocular pressure and brain volumes.

[b]Model 1 was unadjusted model; Model 2 was adjusted for age and gender; Model 3 was adjusted for Model 2 plus APOE4, education, income, depression, diabetes, alcohol consumption, physical activity, smoking, sleep duration, BMI, HDL-C, LDL-C, and triglycerides; Model 4 was adjusted for Model 3 plus blood pressure, hypertension, and the use of medication for hypertension/glaucoma.

Table 3. Association between systolic blood pressure and brain volumes

Brain volume	Systolic blood pressure (mmHg) Quintile 1, <120.0 (*n* = 7444)	Quintile 2, 120.0–128.0 (*n* = 6717)	Quintile 3, 129.0–137.0 (*n* = 7331)	Quintile 4, 138.0–148.0 (*n* = 7170)	Quintile 5, >148.0 (*n* = 7407)	*P*-value for trend	Each 10-mmHg increment[a]
Total brain							
Volume (mL)	1517 ± 73	1506 ± 71	1492 ± 72	1489 ± 71	1477 ± 69	<0.0001	
β (95% CI), Model 1[b]	Reference	−13.90 (−16.26, −11.54)	−21.69 (−24.00, −19.38)	−28.40 (−30.73, −26.08)	−40.75 (−43.05, −38.45)	<0.0001	−7.88 (−8.30, −7.46)
β (95% CI), Model 2	Reference	−1.35 (−3.36, 0.67)	−1.01 (−3.00, 0.99)	0.67 (−1.37, 2.70)	−0.39 (−2.45, 1.68)	0.62	0.06 (−0.32, 0.43)
β (95% CI), Model 3	Reference	−1.53 (−3.61, 0.56)	−0.27 (−2.36, 1.81)	1.18 (−0.96, 3.33)	0.37 (−1.81, 2.56)	0.17	0.24 (−0.14, 0.63)
β (95% CI), Model 4	Reference	3.16 (−1.33, 7.65)	0.50 (−4.26, 5.26)	6.15 (0.82, 11.47)	8.70 (2.77, 14.62)	0.0032	1.00 (0.19, 1.81)
Gray matter							
Volume (ml)	812 ± 47	801 ± 45	790 ± 47	786 ± 47	777 ± 45	<0.0001	
β (95% CI), Model 1	Reference	−12.60 (−14.13, −11.06)	−20.16 (−21.65, −18.66)	−26.67 (−28.18, −25.17)	−35.60 (−37.10, −34.11)	<0.0001	−6.92 (−7.19, −6.65)
β (95% CI), Model 2	Reference	−1.30 (−2.51, −0.09)	−1.96 (−3.15, −0.76)	−2.06 (−3.28, −0.84)	−3.11 (−4.34, −1.87)	<0.0001	−0.57 (−0.79, −0.34)
β (95% CI), Model 3	Reference	−1.11 (−2.35, 0.13)	−1.13 (−2.37, 0.11)	−1.08 (−2.36, 0.19)	−1.88 (−3.18, −0.58)	0.0133	−0.28 (−0.51, −0.05)
β (95% CI), Model 4	Reference	1.65 (−1.01, 4.32)	−0.80 (−3.63, 2.03)	2.05 (−1.12, 5.22)	2.66 (−0.86, 6.19)	0.15	0.11 (−0.37, 0.59)
White matter							
Volume (ml)	705 ± 41	705 ± 41	702 ± 40	702 ± 41	700 ± 41	<0.0001	
β (95% CI), Model 1	Reference	−1.30 (−2.65, 0.04)	−1.54 (−2.85, −0.22)	−1.73 (−3.05, −0.41)	−5.15 (−6.46, −3.84)	<0.0001	−0.96 (−1.20, −0.72)
β (95% CI), Model 2	Reference	−0.05 (−1.34, 1.25)	0.95 (−0.34, 2.24)	2.73 (1.41, 4.04)	2.72 (1.38, 4.05)	<0.0001	0.62 (0.38, 0.87)
β (95% CI), Model 3	Reference	−0.42 (−1.77, 0.93)	0.86 (−0.49, 2.21)	2.26 (0.88, 3.65)	2.25 (0.84, 3.67)	<0.0001	0.52 (0.27, 0.77)
β (95% CI), Model 4	Reference	1.51 (−1.40, 4.41)	1.30 (−1.78, 4.38)	4.10 (0.65, 7.54)	6.03 (2.20, 9.86)	0.0012	0.89 (0.36, 1.42)
Hippocampus							
Volume (μL)	3868 ± 422	3887 ± 427	3880 ± 436	3861 ± 452	3805 ± 440	<0.0001	
β (95% CI), Model 1	Reference	9.01 (−5.57, 23.59)	8.60 (−5.65, 22.86)	−7.48 (−21.81, 6.86)	−59.69 (−73.91, −45.47)	<0.0001	−12.34 (−14.92, −9.77)
β (95% CI), Model 2	Reference	−2.65 (−16.35, 11.06)	−2.08 (−15.67, 11.52)	−3.26 (−17.13, 10.62)	−19.87 (−33.95, −5.80)	0.0122	−3.83 (−6.40, −1.26)
β (95% CI), Model 3	Reference	−6.53 (−20.73, 7.66)	−1.48 (−15.69, 12.74)	−2.53 (−17.15, 12.08)	−22.24 (−37.13, −7.35)	0.0161	−4.00 (−6.63, −1.37)
β (95% CI), Model 4	Reference	−3.77 (−34.06, 26.53)	1.03 (−31.11, 33.16)	−3.25 (−39.22, 32.71)	−30.95 (−70.96, 9.05)	0.17	−1.63 (−7.12, 3.85)
White matter hyperintensity							
Volume (mL)	0.65 ± 1.01	1.10 ± 1.01	0.97 ± 1.07	1.29 ± 0.94	1.55 ± 1.10	<0.0001	
β (95% CI), Model 1	Reference	0.23 (0.19, 0.27)	0.35 (0.31, 0.39)	0.53 (0.49, 0.57)	0.76 (0.72, 0.80)	<0.0001	0.15 (0.14, 0.16)
β (95% CI), Model 2	Reference	0.11 (0.07, 0.14)	0.15 (0.12, 0.19)	0.24 (0.21, 0.28)	0.33 (0.29, 0.37)	<0.0001	0.07 (0.06, 0.08)
β (95% CI), Model 3	Reference	0.10 (0.06, 0.13)	0.13 (0.09, 0.17)	0.21 (0.17, 0.25)	0.29 (0.25, 0.33)	<0.0001	0.06 (0.05, 0.07)
β (95% CI), Model 4	Reference	0.18 (−0.09, 0.44)	0.01 (−0.26, 0.28)	0.05 (−0.25, 0.36)	0.10 (−0.27, 0.46)	0.9	0.04 (−0.01, 0.09)

(*Continued on next page*)

Table 3. *Continued*

Brain volume	Systolic blood pressure (mmHg) Quintile 1, <120.0 (*n* = 7444)	Quintile 2, 120.0–128.0 (*n* = 6717)	Quintile 3, 129.0–137.0 (*n* = 7331)	Quintile 4, 138.0–148.0 (*n* = 7170)	Quintile 5, >148.0 (*n* = 7407)	*P*-value for trend	Each 10-mmHg increment[a]
Ventricular cerebrospinal fluid							
Volume (mL)	40.7 ± 17.5	44.4 ± 19.6	46.9 ± 19.9	48.0 ± 19.6	51.5 ± 21.4	<0.0001	
β (95% CI), Model 1	Reference	3.80 (3.15, 4.45)	5.30 (4.67, 5.93)	7.65 (7.01, 8.29)	10.69 (10.06, 11.32)	<0.0001	2.09 (1.98, 2.20)
β (95% CI), Model 2	Reference	0.35 (−0.23, 0.93)	−0.27 (−0.85, 0.30)	0.10 (−0.49, 0.68)	0.66 (0.07, 1.26)	0.11	0.14 (0.03, 0.25)
β (95% CI), Model 3	Reference	0.44 (−0.14, 1.02)	−0.18 (−0.76, 0.40)	0.23 (−0.37, 0.83)	0.78 (0.17, 1.39)	<0.0001	0.17 (0.05, 0.28)
β (95% CI), Model 4	Reference	0.40 (−0.18, 0.99)	−0.27 (−0.86, 0.31)	0.04 (−0.56, 0.64)	0.46 (−0.17, 1.08)	0.43	−0.03 (−0.27, 0.20)

[a]General linear regression models were used to estimate the association between systolic blood pressure and brain volumes.

[b]Model 1 was unadjusted model; Model 2 was adjusted for age and gender; Model 3 was adjusted for Model 2 plus APOE4, education, income, depression, diabetes, alcohol consumption, physical activity, smoking, sleep duration, BMI, HDL-C, LDL-C, and triglycerides; Model 4 was adjusted for Model 3 plus IOP, glaucoma, and the use of medication for hypertension/glaucoma.

Table 4. Association between diastolic blood pressure and brain volumes

Brain volume	Diastolic blood pressure (mmHg) Quintile 1, <73.0 (*n* = 7601)	Quintile 2, 73.0–78.0 (*n* = 6525)	Quintile 3, 79.0–83.0 (*n* = 7254)	Quintile 4, 84.0–89.0 (*n* = 7243)	Quintile 5, >89.0 (*n* = 7446)	*P*-value for trend	Each 10-mmHg increment[a]
Total brain							
Volume (mL)	1506 ± 73	1499 ± 76	1494 ± 72	1491 ± 72	1489 ± 70	<0.0001	
β (95% CI), Model 1[†]	Reference	−6.60 (−9.01, −4.20)	−10.08 (−12.41, −7.74)	−16.08 (−18.41, −13.74)	−18.55 (−20.87, −16.22)	<0.0001	−6.48 (−7.23, −5.72)
β (95% CI), Model 2	Reference	−0.39 (−2.39, 1.61)	−1.79 (−3.74, 0.17)	−3.53 (−5.50, −1.56)	−4.34 (−6.31, −2.37)	<0.0001	−1.64 (−2.29, −1.00)
β (95% CI), Model 3	Reference	0.65 (−1.42, 2.73)	−0.67 (−2.71, 1.37)	−2.09 (−4.18, −0.00)	−2.63 (−4.76, −0.50)	0.0014	−1.20 (−1.88, −0.52)
β (95% CI), Model 4	Reference	−2.35 (−6.73, 2.04)	−4.26 (−8.77, 0.24)	−5.72 (−10.70, −0.74)	−4.94 (−10.68, 0.80)	0.0477	−0.38 (−1.80, 1.03)
Gray matter							
Volume (mL)	804 ± 48	796 ± 48	792 ± 47	788 ± 47	785 ± 46	<0.0001	
β (95% CI), Model 1	Reference	−8.02 (−9.59, −6.45)	−10.87 (−12.40, −9.34)	−16.25 (−17.78, −14.72)	−20.07 (−21.59, −18.55)	<0.0001	−6.90 (−7.39, −6.40)
β (95% CI), Model 2	Reference	−1.97 (−3.17, −0.77)	−2.68 (−3.85, −1.51)	−4.08 (−5.26, −2.90)	−5.87 (−7.05, −4.69)	<0.0001	−2.01 (−2.40, −1.63)
β (95% CI), Model 3	Reference	−1.16 (−2.39, 0.08)	−1.52 (−2.74, −0.31)	−2.42 (−3.66, −1.18)	−3.80 (−5.06, −2.53)	<0.0001	−1.31 (−1.71, −0.90)
β (95% CI), Model 4	Reference	−2.21 (−4.82, 0.39)	−3.43 (−6.11, −0.75)	−3.81 (−6.77, −0.85)	−3.25 (−6.66, 0.16)	0.0395	−0.82 (−1.66, 0.02)
White matter							
Volume (mL)	702 ± 41	703 ± 42	702 ± 41	702 ± 40	704 ± 40	0.43	
β (95% CI), Model 1	Reference	1.42 (0.06, 2.77)	0.79 (−0.52, 2.10)	0.18 (−1.14, 1.49)	1.53 (0.22, 2.83)	0.19	0.42 (−0.00, 0.85)
β (95% CI), Model 2	Reference	1.58 (0.29, 2.87)	0.89 (−0.37, 2.15)	0.55 (−0.72, 1.82)	1.53 (0.26, 2.80)	0.14	0.37 (−0.05, 0.78)
β (95% CI), Model 3	Reference	1.81 (0.46, 3.16)	0.85 (−0.47, 2.17)	0.33 (−1.03, 1.68)	1.16 (−0.22, 2.54)	0.55	0.11 (−0.33, 0.55)
β (95% CI), Model 4	Reference	−0.13 (−2.96, 2.70)	−0.83 (−3.74, 2.08)	−1.92 (−5.14, 1.30)	−1.69 (−5.40, 2.02)	0.24	0.43 (−0.49, 1.35)
Hippocampus							
Volume (μL)	3839 ± 426	3845 ± 427	3868 ± 453	3858 ± 438	3885 ± 436	0.00163	
β (95% CI), Model 1	Reference	19.44 (4.81, 34.08)	21.77 (7.54, 36.01)	19.40 (5.16, 33.64)	35.21 (21.07, 49.36)	<0.0001	12.27 (7.66, 16.87)
β (95% CI), Model 2	Reference	5.78 (−7.88, 19.43)	1.14 (−12.19, 14.47)	−7.47 (−20.90, 5.97)	−3.69 (−17.13, 9.74)	0.2	−2.05 (−6.44, 2.34)
β (95% CI), Model 3	Reference	4.67 (−9.49, 18.83)	−4.43 (−18.34, 9.49)	−9.87 (−24.12, 4.38)	−8.77 (−23.28, 5.74)	0.0623	−4.66 (−9.28, −0.03)
β (95% CI), Model 4	Reference	−13.78 (−43.36, 15.81)	13.01 (−17.37, 43.40)	3.54 (−30.08, 37.15)	19.38 (−19.38, 58.13)	0.25	2.18 (−7.40, 11.75)
White matter hyperintensity							
Volume (mL)	0.84 ± 1.12	0.97 ± 0.98	1.06 ± 1.01	1.22 ± 1.01	1.45 ± 1.12	<0.0001	
β (95% CI), Model 1	Reference	0.13 (0.09, 0.17)	0.23 (0.19, 0.27)	0.35 (0.30, 0.39)	0.50 (0.46, 0.54)	<0.0001	0.18 (0.17, 0.19)
β (95% CI), Model 2	Reference	0.07 (0.04, 0.11)	0.15 (0.11, 0.19)	0.23 (0.19, 0.26)	0.37 (0.34, 0.41)	<0.0001	0.14 (0.13, 0.15)
β (95% CI), Model 3	Reference	0.07 (0.03, 0.10)	0.13 (0.09, 0.17)	0.19 (0.15, 0.23)	0.33 (0.29, 0.37)	<0.0001	0.13 (0.11, 0.14)
β (95% CI), Model 4	Reference	0.11 (−0.14, 0.36)	0.12 (−0.15, 0.39)	0.21 (−0.09, 0.51)	0.39 (0.04, 0.73)	0.0386	0.13 (0.05, 0.21)

(*Continued on next page*)

Table 4. *Continued*

Brain volume	Diastolic blood pressure (mmHg) Quintile 1, <73.0 (*n* = 7601)	Quintile 2, 73.0–78.0 (*n* = 6525)	Quintile 3, 79.0–83.0 (*n* = 7254)	Quintile 4, 84.0–89.0 (*n* = 7243)	Quintile 5, >89.0 (*n* = 7446)	*P*-value for trend	Each 10-mmHg increment[a]
Ventricular cerebrospinal fluid							
Volume (mL)	43.9 ± 19.2	45.42 ± 21.0	46.3 ± 192	47.5 ± 20.1	48.9 ± 20.1	<0.0001	
β (95% CI), Model 1	Reference	1.85 (1.20, 2.51)	2.57 (1.93, 3.21)	3.84 (3.21, 4.48)	5.34 (4.70, 5.97)	<0.0001	1.84 (1.64, 2.05)
β (95% CI), Model 2	Reference	0.01 (−0.56, 0.59)	0.08 (−0.49, 0.64)	0.14 (−0.43, 0.71)	1.03 (0.46, 1.59)	0.0009	0.36 (0.18, 0.55)
β (95% CI), Model 3	Reference	0.12 (−0.46, 0.70)	0.25 (−0.32, 0.82)	0.32 (−0.26, 0.90)	1.26 (0.67, 1.86)	0.0001	0.45 (0.26, 0.65)
β (95% CI), Model 4	Reference	0.10 (−0.48, 0.68)	0.17 (−0.40, 0.74)	0.18 (−0.40, 0.77)	0.99 (0.38, 1.60)	0.0038	0.13 (−0.28, 0.55)

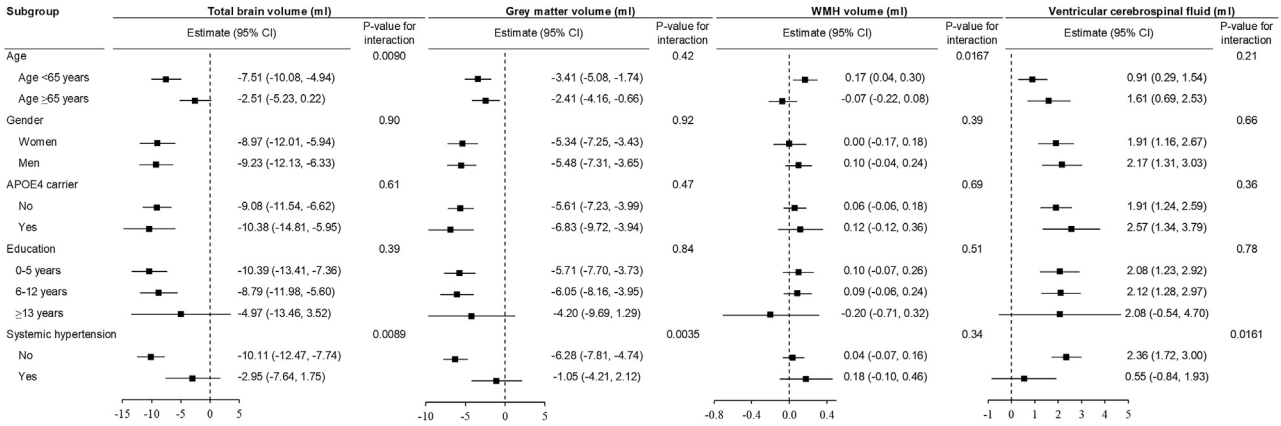


Figure 2. Moderation analysis for the association between intraocular pressure and brain volume APOE4 = apolipoprotein E ε4; CI = confidence interval; WMH = white matter hyperintensity

General linear regression models were used to examine whether associations between intraocular pressure and brain volumes were moderated by age, gender, APOE4, education, or systemic hypertension. Analysis was adjusted for age, gender, education, income, smoking, physical activity, alcohol consumption, and sleep duration. Horizontal lines indicate the ranges of the 95% CIs and the vertical dash lines indicate the mean of 0.0.

ventricular cerebrospinal fluid volume (0.67 mL, 0.14 to 1.21, Table S16). The results from the MRlap analysis were consistent with those from the main analysis using IVW. IOP was associated with reduced volumes of total brain and gray matter, as well as an increased volume of ventricular cerebrospinal fluid (Figure S4). In the inverse probability weighting analysis, β (95% CI) for total brain (mL), gray mater (mL), and WMH volumes associated with each 10-mmHg increment of DBP were −0.97 mL (−1.67 to −0.27), −1.07 (−1.49 to −0.65), and 0.11 mL (0.10–0.13), respectively (Table S17). Furthermore, increased SBP was associated with a smaller hippocampal volume (β (95% CI) for each 10-mmHg increment of SBP: −2.82 mL, −5.51 to −0.14, and higher WMH load (0.05 mL, 0.04 to 0.06), Table S18). MR analyses showed that the effect of the hippocampus on BP was minimal with each 100 μL increase in the hippocampus associated with 0.2–0.6 mmHg increase in SBP and 0.1 to 0.4 mmHg increase in DBP. No other significant associations were observed (Figure S5).

DISCUSSION

In this large cohort study of community-dwelling adults, we found higher IOP was associated with reduced volumes of total brain and gray matter in the phenotypic analysis dependent on BP and the use of medication for glaucoma. This association was confirmed by the genetic analysis. Increased SBP was associated with smaller brain volumes whereas these associations were attenuated to be non-significant or even reversed after adjustment for the use of antihypertensive medication. Increased DBP was associated with higher WMH load in the phenotypic analysis independent of the use of antihypertensive medication and IOP and this association was confirmed in the genetic analysis. The association between IOP and volumes of total brain and WMH was stronger in younger than in older individuals and increased IOP was associated with smaller volumes of total brain and gray matter in those free of systemic hypertension only. The association between DBP/SBP and volumes of total brain, gray matter, and WMH was stronger in younger individuals, women, and lowly educated individuals. In contrast, genetic analyses revealed that brain volumes had minimal effect on BP, and no effect on IOP was found.

A continuous supply of oxygen and glucose from the blood to the brain is fundamental for brain health, but increased arterial stiffness caused by hypertension[17] may decrease cerebral blood flow[18–20] thus resulting in brain damage. Numerous observational studies have examined the association between hypertension and brain volume.[9,21,22] Strong evidence has suggested a positive association between BP and WMH,[9,22,23] but findings regarding the association between BP, total brain volume, and hippocampal volume are inconsistent between previous studies.[23] We found increased SBP was associated with smaller hippocampal volume and increased DBP was associated with smaller volumes of total brain and gray matter and higher WMH load. Only the association between DBP and WMH load remained significant after adjustment for IOP, glaucoma, and the use of medication for hypertension/glaucoma. This is consistent with previous studies indicating that DBP, rather than SBP, was more significant for the development of WMH[22,24] Similarly, only the association between DBP and WMH load was confirmed by MR analyses. This is consistent with a recent meta-analysis of seven clinical trials showing that antihypertensive treatment is beneficial for WMH changes but not for total brain atrophy.[25] Whilst WMH than other regions of the brain is more predictive of cognitive impairment and dementia.26 Therefore, our findings highlight the importance of DBP lowering in the prevention of dementia.

Increasing evidence suggests that vision impairment especially that caused by glaucoma is associated with changes in the brain,[26,27] however, less is known regarding the association between IOP and brain volume. Previous studies have demonstrated a high correlation between IOP and intracranial pressure[28,29] suggesting that IOP might be predictive of brain volumes. In another way, increased IOP may damage the optic nerve thus reducing its ability to transmit information to the brain, ultimately resulting in brain volume loss. It remains debatable regarding the causal relationships of IOP with brain volumes.[14] We found increased IOP was associated with smaller volumes of total brain and gray matter measured over 7 years later. MR analyses showed that increased IOP is linked to gray matter volume loss. This is consistent with a growing amount of literature

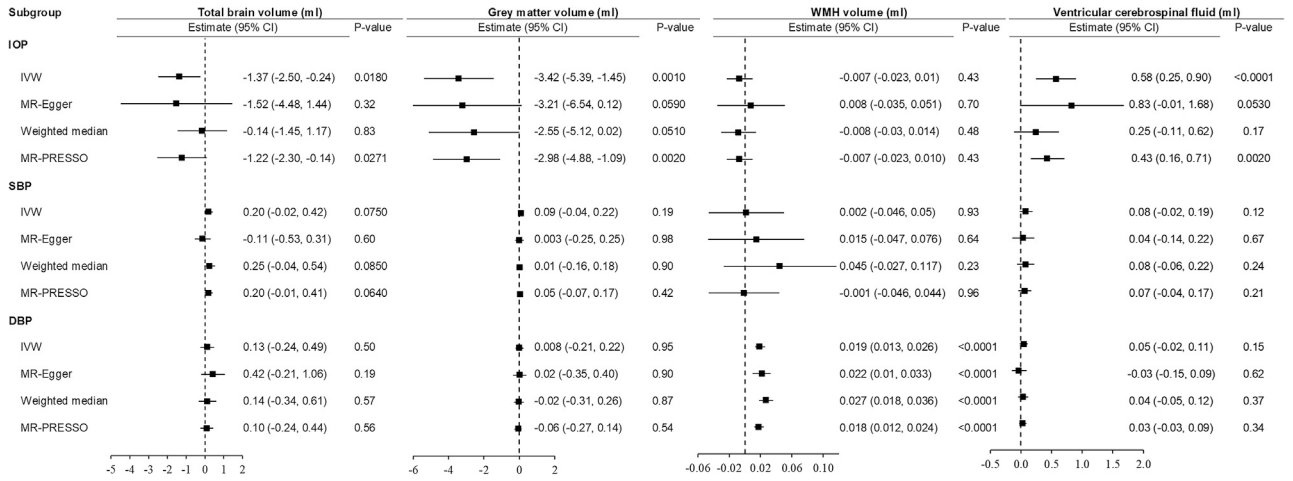


Figure 3. Mendelian randomization analyses for the effect of intraocular pressure and blood pressure on brain volumes CI = confidence interval; DBP = diastolic blood pressure; IOP = intraocular pressure; IVW = inverse-variance weighting; MR-PRESSO = Mendelian Randomization Pleiotropy Residual Sum and Outlier; MR-Egger = Mendelian randomization Egger; SBP = systolic blood pressure; WMH = white matter hyperintensity

Horizontal lines indicate the ranges of the 95% CIs and the vertical dash lines indicate the mean of 0.0.

suggesting that glaucoma affects the brain *trans*-synaptically.[14,15] Recent research has demonstrated that gray matter volume may be a reliable marker to track disease progression in dementia,31 thus IOP may help identify individuals at higher risk of brain atrophy.

We found the association between IOP and volumes of total brain and WMH was more prominent in younger than in older individuals. However, no prior analysis has investigated the association between intraocular pressure (IOP) and brain volumes stratified by age. While IOP is highly correlated with blood pressure (BP), previous studies have demonstrated that hypertension diagnosed at a younger age was associated with a larger reduction in brain volume.[8,30] This may partly explain why the association between IOP and total brain volume is more prominent in younger individuals. The association between IOP and brain volume was stronger in those free of systemic hypertension. The underlying mechanisms are unclear, but a previous study suggests the association between main eye diseases and dementia was stronger among those without systemic diseases.[31] The lower rate of diagnosis and treatment of hypertension among younger individuals may also explain why the association was stronger among those without hypertension. We also found the association between BP and total brain volume was stronger among individuals with lower education. This may be explained by the fact that individuals who were highly educated were more likely to seek health care and thus less likely to result in brain volume loss with aging BP appears to be more predictive of brain volumes in women than in men, which needs to be confirmed in future research.

Our findings suggest the effect sizes of BP and IOP might be relatively small, and the use of anti-glaucoma or antihypertensive medications, or other treatments might minimize the risk of neurological or cognitive disorders because of these small effects on brain volume maintenance in the aging population. To our knowledge, this is the first study to examine the association of IOP and BP with brain volumes in both observational and MR analyses.

In conclusion, according to our results, higher IOP is associated with a gray matter volume while increased DBP is linked to higher WMH load. Younger individuals and those without hypertension are more in need of care for the prevention of brain volume reduction potentially via IOP lowering. The association between BP and brain volume reduction is stronger among younger individuals, women, and lowly educated individuals.

Limitations of the study

Our study has several potential limitations. Firstly, MRI and IOP data were collected in a small subgroup of the UK Biobank cohort, which may limit the generalizability of our findings to the whole population. However, the inverse probability weighting analysis showed similar results to the main findings. Secondly, intracranial pressure is an important confounder for the association between IOP and brain volumes; however, it is not adjusted for in our analysis as data on intracranial pressure are not available in our study. Thirdly, the sample overlap between the GRS analyses for IOP and the GWAS from which the summary statistics were derived might have resulted in a small bias in the association between the GRS for IOP and brain volumes. Fourthly, the analysis was conducted among individuals of European ancestry such that the findings may not be applied to other ethnic groups.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Dr. Xianwen Shang (xianwen.shang@polyu.edu.hk).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- UKBiobank data are available in a public, open access repository (https://www.ukbiobank.ac.uk/). GWAS Summary statistics of IOP is available at https://www.ebi.ac.uk/gwas/studies/GCST006412. GWAS Summary statistics of BP are available at https://www.ebi.ac.uk/gwas/studies/GCST006624 And https://www.ebi.ac.uk/gwas/studies/GCST006630.
- This article does not report the original code.
- Any additional information required to reanalyze the data reported in this article is available from the lead contact upon request.

ACKNOWLEDGMENTS

This research was conducted using the UK Biobank resource. We thank the participants of the UK Biobank. ChatGPT was used to check for typos or grammar errors in the article.

We acknowledge the following funding resources.

XS receives support from Postdoctoral Research Funds of Guangdong Provincial People's Hospital (BY012021047). ZZ receives support from the National Natural Science Foundation of China (82101173, 81870663, 82171075), the Research Foundation of Medical Science and Technology of Guangdong Province (B2021237). HY receives support from the Research Foundation of Medical Science and Technology of Guangdong Province, China (A2022323); NSFC Incubation Project of Guangdong Provincial People's Hospital, China (KY0120220051), NSFC Young Scientist Found (82301246), the Outstanding Young Talent Trainee Program of Guangdong Provincial People's Hospital (KJ012019087), Guangdong Provincial People's Hospital Scientific Research Funds for Leading Medical Talents and Distinguished Young Scholars in Guangdong Province (KJ012019457), Talent Introduction Fund of Guangdong Provincial People's Hospital (Y012018145). MH receives support from the High-level Talent Flexible Introduction Fund of Guangdong Provincial People's Hospital (No. KJ012019530). MH also receives support from the University of Melbourne at Research Accelerator Program and the CERA Foundation. The Center for Eye Research Australia receives Operational Infrastructure Support from the Victorian State Government. The sponsor or funding organization had no role in the design or conduct of this research. The sponsor or funding organization had no role in the design, conduct, analysis, or reporting of this study. The funding sources did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; and decision to submit the article for publication.

AUTHOR CONTRIBUTIONS

Conception and design of the study: XS, YH, HY, XY, and MH. Acquisition and analysis of data: XS, YH, SZ, ZZ, XLZ, XYZ, and JHL.Writing - original draft: XS and YH. Writing - review and editing: XS, YH, ZZ, XLZ, WW, XYZ, JL, JHL, ST, ZG, YJH, HY, XY, and MH. Figure drafting: XS, HY, and JL.

DECLARATION OF INTERESTS

The authors declare that they have no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110817.

Received: January 25, 2024
Revised: April 22, 2024
Accepted: August 22, 2024
Published: August 29, 2024

REFERENCES

1. GBD 2016 Neurology Collaborators (2019). Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. *18*, 459–480. https://doi.org/10.1016/s1474-4422(18)30499-x.
2. Sweeney, M.D., Kisler, K., Montagne, A., Toga, A.W., and Zlokovic, B.V. (2018). The role of brain vasculature in neurodegenerative disorders. Nat. Neurosci. *21*, 1318–1331. https://doi.org/10.1038/s41593-018-0234-x.
3. Wang, M., Roussos, P., McKenzie, A., Zhou, X., Kajiwara, Y., Brennand, K.J., De Luca, G.C., Crary, J.F., Casaccia, P., Buxbaum, J.D., et al. (2016). Integrative network analysis of nineteen brain regions identifies molecular signatures and networks underlying selective regional vulnerability to Alzheimer's disease. Genome Med. *8*, 104. https://doi.org/10.1186/s13073-016-0355-3.
4. Jacobsen, C., Hagemeier, J., Myhr, K.M., Nyland, H., Lode, K., Bergsland, N.,

Ramasamy, D.P., Dalaker, T.O., Larsen, J.P., Farbu, E., and Zivadinov, R. (2014). Brain atrophy and disability progression in multiple sclerosis patients: a 10-year follow-up study. J. Neurol. Neurosurg. Psychiatry *85*, 1109–1115. https://doi.org/10.1136/jnnp-2013-306906.

5. Mitchell, T., Lehéricy, S., Chiu, S.Y., Strafella, A.P., Stoessl, A.J., and Vaillancourt, D.E. (2021). Emerging Neuroimaging Biomarkers Across Disease Stage in Parkinson Disease: A Review. JAMA Neurol. *78*, 1262–1272. https://doi.org/10.1001/jamaneurol.2021.1312.
6. Nakazawa, T., Ohara, T., Hirabayashi, N., Furuta, Y., Hata, J., Shibata, M., Honda, T., Kitazono, T., Nakao, T., and Ninomiya, T. (2022). Multiple-region grey matter atrophy as a predictor for the development of dementia in a community: the Hisayama Study. J. Neurol. Neurosurg. Psychiatry *93*, 263–271. https://doi.org/10.1136/jnnp-2021-326611.
7. Cox, S.R., Lyall, D.M., Ritchie, S.J., Bastin, M.E., Harris, M.A., Buchanan, C.R., Fawns-Ritchie, C., Barbu, M.C., de Nooij, L., Reus, L.M., et al. (2019). Associations between vascular risk factors and brain MRI indices in UK Biobank. Eur. Heart J. *40*, 2290–2300. https://doi.org/10.1093/eurheartj/ehz100.
8. Shang, X., Hill, E., Zhu, Z., Liu, J., Ge, B.Z., Wang, W., and He, M. (2021). The Association of Age at Diagnosis of Hypertension With Brain Structure and Incident Dementia in the UK Biobank. Hypertension *78*, 1463–1474. https://doi.org/10.1161/hypertensionaha.121.17608.
9. Lane, C.A., Barnes, J., Nicholas, J.M., Sudre, C.H., Cash, D.M., Parker, T.D., Malone, I.B., Lu, K., James, S.N., Keshavan, A., et al. (2019). Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. Lancet Neurol. *18*, 942–952. https://doi.org/10.1016/s1474-4422(19)30228-5.
10. Muller, M., Sigurdsson, S., Kjartansson, O., Aspelund, T., Lopez, O.L., Jonnson, P.V., Harris, T.B., van Buchem, M., Gudnason, V., and Launer, L.J. (2014). Joint effect of mid- and late-life blood pressure on the brain: the AGES-Reykjavik study. Neurology *82*, 2187–2195. https://doi.org/10.1212/wnl.0000000000000517.
11. Wu, S.Y., and Leske, M.C. (1997). Associations with intraocular pressure in the Barbados Eye Study. Arch. Ophthalmol. *115*, 1572–1576. https://doi.org/10.1001/archopht.1997.01100160742012.
12. Memarzadeh, F., Ying-Lai, M., Azen, S.P., and Varma, R.; Los Angeles Latino Eye Study Group (2008). Associations with intraocular pressure in Latinos: the Los Angeles Latino Eye Study. Am. J. Ophthalmol. *146*, 69–76. https://doi.org/10.1016/j.ajo.2008.03.015.
13. Chan, M.P.Y., Grossi, C.M., Khawaja, A.P., Yip, J.L.Y., Khaw, K.T., Patel, P.J., Khaw, P.T., Morgan, J.E., Vernon, S.A., and Foster, P.J.; UK Biobank Eye and Vision Consortium (2016). Associations with Intraocular Pressure in a Large Cohort: Results from the UK Biobank. Ophthalmology *123*, 771–782. https://doi.org/10.1016/j.ophtha.2015.11.031.
14. Lawlor, M., Danesh-Meyer, H., Levin, L.A., Davagnanam, I., De Vita, E., and Plant, G.T. (2018). Glaucoma and the brain: Trans-synaptic degeneration, structural change, and implications for neuroprotection. Surv. Ophthalmol. *63*, 296–306. https://doi.org/10.1016/j.survophthal.2017.09.010.
15. Sponsel, W.E., Groth, S.L., Satsangi, N., Maddess, T., and Reilly, M.A. (2014). Refined Data Analysis Provides Clinical Evidence for Central Nervous System Control of Chronic Glaucomatous Neurodegeneration. Transl. Vis. Sci. Technol. *3*, 1. https://doi.org/10.1167/tvst.3.3.1.
16. Davey Smith, G., and Ebrahim, S. (2005). What can mendelian randomisation tell us about modifiable behavioural and environmental exposures? BMJ *330*, 1076–1079. https://doi.org/10.1136/bmj.330.7499.1076.
17. Dumor, K., Shoemaker-Moyle, M., Nistala, R., and Whaley-Connell, A. (2018). Arterial Stiffness in Hypertension: an Update. Curr. Hypertens. Rep. *20*, 72. https://doi.org/10.1007/s11906-018-0867-x.
18. Jefferson, A.L., Cambronero, F.E., Liu, D., Moore, E.E., Neal, J.E., Terry, J.G., Nair, S., Pechman, K.R., Rane, S., Davis, L.T., et al. (2018). Higher Aortic Stiffness Is Related to Lower Cerebral Blood Flow and Preserved Cerebrovascular Reactivity in Older Adults. Circulation *138*, 1951–1962. https://doi.org/10.1161/circulationaha.118.032410.
19. Jefferson, A.L. (2020). Midlife Consequences of Cumulative Blood Pressure Exposure: Importance of a Lifespan Approach. Circulation *141*, 725–727. https://doi.org/10.1161/circulationaha.120.044447.
20. Pase, M.P., Himali, J.J., Mitchell, G.F., Beiser, A., Maillard, P., Tsao, C., Larson, M.G., DeCarli, C., Vasan, R.S., and Seshadri, S. (2016). Association of Aortic Stiffness With Cognition and Brain Aging in Young and Middle-Aged Adults: The Framingham Third Generation Cohort Study. Hypertension *67*, 513–519. https://doi.org/10.1161/hypertensionaha.115.06610.
21. Maillard, P., Seshadri, S., Beiser, A., Himali, J.J., Au, R., Fletcher, E., Carmichael, O., Wolf, P.A., and DeCarli, C. (2012). Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. Lancet Neurol. *11*, 1039–1047. https://doi.org/10.1016/s1474-4422(12)70241-7.
22. Wartolowska, K.A., and Webb, A.J.S. (2021). Midlife blood pressure is associated with the severity of white matter hyperintensities: analysis of the UK Biobank cohort study. Eur. Heart J. *42*, 750–757. https://doi.org/10.1093/eurheartj/ehaa756.
23. Alateeq, K., Walsh, E.I., and Cherbuin, N. (2021). Higher Blood Pressure is Associated with Greater White Matter Lesions and Brain Atrophy: A Systematic Review with Meta-Analysis. J. Clin. Med. *10*, 637. https://doi.org/10.3390/jcm10040637.
24. Godin, O., Tzourio, C., Maillard, P., Mazoyer, B., and Dufouil, C. (2011). Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes: the Three-City (3C)-Dijon Magnetic Resonance Imaging Study. Circulation *123*, 266–273. https://doi.org/10.1161/circulationaha.110.961052.
25. Su, C., Wu, H., Yang, X., Zhao, B., and Zhao, R. (2021). The relation between antihypertensive treatment and progression of cerebral small vessel disease: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltim.) *100*, e26749. https://doi.org/10.1097/md.0000000000026749.
26. Frezzotti, P., Giorgio, A., Toto, F., De Leucio, A., and De Stefano, N. (2016). Early changes of brain connectivity in primary open angle glaucoma. Hum. Brain Mapp. *37*, 4581–4596. https://doi.org/10.1002/hbm.23330.
27. Wang, R., Tang, Z., Sun, X., Wu, L., Wang, J., Zhong, Y., and Xiao, Z. (2018). White Matter Abnormalities and Correlation With Severity in Normal Tension Glaucoma: A Whole Brain Atlas-Based Diffusion Tensor Study. Invest. Ophthalmol. Vis. Sci. *59*, 1313–1322. https://doi.org/10.1167/iovs.17-23597.
28. Sheeran, P., Bland, J.M., and Hall, G.M. (2000). Intraocular pressure changes and alterations in intracranial pressure. Lancet *355*, 899. https://doi.org/10.1016/s0140-6736(99)02768-3.
29. Lashutka, M.K., Chandra, A., Murray, H.N., Phillips, G.S., and Hiestand, B.C. (2004). The relationship of intraocular pressure to intracranial pressure. Ann. Emerg. Med. *43*, 585–591. https://doi.org/10.1016/j.annemergmed.2003.12.006.
30. Pase, M.P., Davis-Plourde, K., Himali, J.J., Satizabal, C.L., Aparicio, H., Seshadri, S., Beiser, A.S., and DeCarli, C. (2018). Vascular risk at younger ages most strongly associates with current and future brain volume. Neurology *91*, e1479–e1486. https://doi.org/10.1212/wnl.0000000000006360.
31. Shang, X., Zhu, Z., Huang, Y., Zhang, X., Wang, W., Shi, D., Jiang, Y., Yang, X., and He, M. (2023). Associations of ophthalmic and systemic conditions with incident dementia in the UK Biobank. Br. J. Ophthalmol. *107*, 275–282. https://doi.org/10.1136/bjophthalmol-2021-319508.
32. Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M., et al. (2015). UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. *12*, e1001779. https://doi.org/10.1371/journal.pmed.1001779.
33. Smith, S.M., Zhang, Y., Jenkinson, M., Chen, J., Matthews, P.M., Federico, A., and De Stefano, N. (2002). Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage *17*, 479–489. https://doi.org/10.1006/nimg.2002.1040.
34. Debette, S., Schilling, S., Duperron, M.G., Larsson, S.C., and Markus, H.S. (2019). Clinical Significance of Magnetic Resonance Imaging Markers of Vascular Brain Injury: A Systematic Review and Meta-analysis. JAMA Neurol. *76*, 81–94. https://doi.org/10.1001/jamaneurol.2018.3122.
35. Yamazaki, Y., Zhao, N., Caulfield, T.R., Liu, C.C., and Bu, G. (2019). Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat. Rev. Neurol. *15*, 501–518. https://doi.org/10.1038/s41582-019-0228-7.
36. Khawaja, A.P., Cooke Bailey, J.N., Wareham, N.J., Scott, R.A., Simcoe, M., Igo, R.P., Jr., Song, Y.E., Wojciechowski, R., Cheng, C.Y., Khaw, P.T., et al. (2018). Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma. Nat. Genet. *50*, 778–782. https://doi.org/10.1038/s41588-018-0126-8.
37. Evangelou, E., Warren, H.R., Mosen-Ansorena, D., Mifsud, B., Pazoki, R., Gao, H., Ntritsos, G., Dimou, N., Cabrera, C.P.,

Karaman, I., et al. (2018). Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nat. Genet. *50*, 1412–1425. https://doi.org/10.1038/s41588-018-0205-x.

38. Chang, C.C., Chow, C.C., Tellier, L.C., Vattikuti, S., Purcell, S.M., and Lee, J.J. (2015). Second-generation PLINK: rising to the challenge of larger and richer datasets. GigaScience *4*, 7. https://doi.org/10.1186/s13742-015-0047-8.
39. Bowden, J., Del Greco M, F., Minelli, C., Davey Smith, G., Sheehan, N.A., and Thompson, J.R. (2016). Assessing the suitability of summary data for two-sample Mendelian randomization analyses using MR-Egger regression: the role of the I2 statistic. Int. J. Epidemiol. *45*, 1961–1974. https://doi.org/10.1093/ije/dyw220.
40. Verbanck, M., Chen, C.Y., Neale, B., and Do, R. (2018). Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat. Genet. *50*, 693–698. https://doi.org/10.1038/s41588-018-0099-7.
41. Hernán, M.A., and Robins, J.M. (2006). Estimating causal effects from epidemiological data. J. Epidemiol. Community Health *60*, 578–586. https://doi.org/10.1136/jech.2004.029496.
42. Mounier, N., and Kutalik, Z. (2023). Bias correction for inverse variance weighting Mendelian randomization. Genet. Epidemiol. *47*, 314–331. https://doi.org/10.1002/gepi.22522.
43. Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. J. Roy. Stat. Soc. Ser. *57*, 289–300.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
UK Biobank dataset	https://biobank.ctsu.ox.ac.uk	The UK Biobank data access has been approved under the project title ''Regulators of the association between ocular disorders and systemic diseases.". The approval number is 86091.
GWAS Summary statistics of IOP	https://www.ebi.ac.uk/gwas/studies/GCST006412	When assessing the genetic relationship between IOP and brain volume, genetic variants associated with IOP were selected from a GWAS of 139,555 European participants on IOP.
GWAS Summary statistics of blood pressure	https://www.ebi.ac.uk/gwas/studies/GCST006624 And https://www.ebi.ac.uk/gwas/studies/GCST006630	When assessing the genetic relationship between blood pressure and brain volume, genetic variants associated with SBP/DBP were selected from GWASs on SBP/DBP.
Software and algorithms		
SAS 9.4 for Windows	https://www.sas.com/en_gb/home.html?utm_source=google&utm_medium=cpc&utm_campaign=brand-global&utm_content=GMS-88251&gad_source=1&gclid=CjwKCAjwhvi0BhA4EiwAX25uj-A9C49oHBWDZ0Aq65LD-9UDXEpQ2_PGcCujM6nQdIny6jCUmT0q1BoCVVQQAvD_BwE	Data analyses for the non-MR study were conducted using SAS 9.4 for Windows.
PLINK 2.0.	https://www.cog-genomics.org/plink/2.0/	PLINK was used to perform GWAS on brain volumn and generate GRS.
MR package in R (version 4.0.3)	https://mrcieu.github.io/TwoSampleMR/articles/introduction.html	Inverse-variance weighting (IVW), MR-Egger regression (MR-Egger), and weighted median were performed using MR package.
MR-PRESSO	https://github.com/rondolab/MR-PRESSO	Sensitivity analyses were performed using MR-Pleiotropy Residual Sum and Outlier method (MR-PRESSO), which detects and excludes SNPs with potential pleiotropic effects
MRlap	https://github.com/n-mounier/MRlap	Since there is an overlap between the participants in our two-sample MR analysis and those in the GWAS from which we obtained the summary statistics, we used MRlap to correct the bias in IVW for the MR analysis

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Our analysis was based on the UK Biobank cohort of more than 500,000 participants aged 40-70 years at baseline between 2006 and 2010.[32] The design of the study has been detailed elsewhere.[32] The UK Biobank Study's ethical approval had been granted by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee. All participants provided informed consent through electronic signature at baseline assessment.

Ethics approval and consent to participate

The UK Biobank Study's ethical approval had been granted by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee. All participants provided informed consent through electronic signature at baseline assessment.

METHOD DETAILS

Brain magnetic resonance imaging

Magnetic resonance imaging (MRI) assessment was conducted between August 2014 and October 2019. A standard Siemens Skyra 3T scanner with a standard 32-channel radio-frequency receiver head coil was used to collect MRI data.[33] T1- and T2-weighted scans were analysed with the Functional MRI of the Brain Software Library. Volumes of total brain, grey matter, white matter, white matter hyperintensity (WMH), and hippocampus were assessed. Total brain volume was calculated by summing the grey matter and white matter volumes (excludes cerebrospinal fluid). Brain volumes were normalized for head size based on the external surface of the skull, using the ratio-corrected method.[33] The hyperintensities indicate abnormalities in the white matter, often associated with small vessel disease or other pathological processes.[34] Given the positively skewed distribution, WMH was logarithm-transformed in our analysis.[22]

Assessment of intraocular pressure and systemic blood pressure

IOP was measured once for each eye using an Ocular Response Analyzer noncontact tonometer (Reichert Corp) at baseline (2009). Data on both Goldman-correlated and corneal-compensated IOP were collected. We used Goldman-correlated IOP in the analysis as it is considered the standard for measurement of IOP. The average of the right and left eye IOP measurements were used in the analysis. We used one eye's IOP value as the participant's IOP if data were available for only one eye.

BP was measured at three surveys (2006-2010, 2012-2013, and 2014-2019). Within each survey, BP was measured twice using a digital sphygmomanometer (Omron 705 IT; OMRON Healthcare Europe B.V., Hoofddorp, Netherlands) by trained nurses. We used the average of the two measurements in the analysis. BP measured concurrently with IOP was used in the analysis. Hypertension was defined by SBP $\geq$140 mmHg or diastolic BP (DBP) $\geq$90 mmHg, or as those who reported a diagnosis of hypertension.

Covariates

Weight was measured using a Tanita BC-418MA body composition analyser (Tanita Corporation, Arlington Heights, IL) and height was measured in a barefoot standing position using the Saca 202 device. BMI was computed as weight (kilograms) divided by height squared (meters). A touchscreen computer was used to collect information including age, gender, ethnicity, education, household income, smoking, alcohol consumption, and sleep duration. Questions about physical activity, which were similar to those used in the short form of the International Physical Activity Questionnaire, were used to estimate excess metabolic equivalent (MET)-hours/week of physical activity during work and leisure time.

Data on glaucoma, depression, and the use of medication for glaucoma/hypertension at baseline were collected using a self-reported questionnaire. Lipids including total cholesterol, HDL-C, LDL-C, and triglycerides were tested by direct enzymatic methods (Konelab, Thermo Fisher Scientific, Waltham, Massachusetts). Glycated haemoglobin (HbA1c) was measured using high-performance liquid chromatography on a Bio-Rad Variant II Turbo. Apolipoprotein E ε4 (APOE4) + dominant model of ε3/ε4 and ε4/ε4 was used to define the presence of APOE4.[35]

Genetic data

BiLEVE Axiom array, or the UK Biobank Axiom array was used for genotyping by Affymetrix and ~450,000 of the ~500,000 UK Biobank participants were genotyped. Prior to data release, genotype imputation using the Haplotype Reference Consortium reference panel was conducted by the UK Biobank researchers and then followed by extensive quality control.

Mendelian randomization: Instrumental variable selection and genome-wide associated study summary statistics

When assessing the genetic relationship between IOP and brain volume, genetic variants associated with IOP were selected from a Genome-wide associated study (GWAS) of 139,555 European participants. From this study, 133 single nucleotide polymorphisms (SNPs) associated with IOP with a p < 5e-08 and r^2 < 0.01 were used as IVs in MR analyses.[36] The SNP-exposure regression coefficients used in these MR analyses were their effect on IOP from the abovementioned GWAS; the SNP-outcome regression coefficients were obtained from our analysis of the association between 133 individual SNPs and different brain volumes (Tables 1 and S6).

When assessing the genetic relationship between BP and brain volume, IVs for SBP and DBP were selected from GWASs involving over one million European participants obtained from International Consortium for Blood Pressure.[37] SNPs with a p < 5e-08 and r^2 < 0.01 were selected, leading to 406 valid SNPs used as IVs for SBP and 476 SNPs for DBP. The SNP-exposure regression coefficients used in these MR analyses were their effect on SBP/DBP from the previous GWAS[37]; the SNP-outcome regression coefficients were obtained from our analysis of the association between individual selected SBP/DBP SNPs and different brain volumes (Tables S7 and S11).

Genetic association with brain volume

As a sensitivities analysis, the effect of brain volumes on IOP/BP was assessed. GWASs were performed for six individual brain volume traits in a sample of 3,8402 unrelated participants of European ancestry in the UK Biobank cohort using PLINK 2.0.[38] We included 6,133,593 genetic variants with minor allele frequency (MAF) $\geq$1%, missing genotype call rate <5% and Hardy-Weinberg equilibrium p-value < 1.0×10^{-6} and imputation info score > 0.8. For each of the six brain volume traits, IVs were selected from our GWAS summary statistics using the following criteria: SNP situated at least 250 kb apart and with pairwise linkage disequilibrium (LD) r^2 < 0.01 that were associated with brain volume trait at genome-wide statistical significance level (p < 5.0e-08). We used a linear regression model to test the association between each SNP and

individual brain volume traits, adjusting for age, sex, and the first 10 ancestry principal components. A total number of 29 SNPs, 16 SNPs for grey matter, 29 SNPs for white matter, 12 SNPs for white matter hyperintensity, 40 SNPs for hippocampus, and 150 SNPs for ventricular cerebrospinal fluid volume were selected as IVs for volumes of total brain. In the MR analyses, the SNP-exposure coefficients were derived from our GWAS analysis and SNP-outcome coefficients were derived from our analysis of the association between selected SNPs for brain volumes and IOP/SBP/DBP.

Generation of the genetic risk score

Separate GRSs were generated for IOP, SBP and DBP based on SNPs in previous GWAS analyses reported by Khawaja and Evangelou.[36,37] GRSs for each participant were computed using the score function implemented in PLINK 2.0.[38]

QUANTIFICATION AND STATISTICAL ANALYSIS

In general, we first conducted observational studies to explore the phenotypic association between brain volume and IOP or BP. To identify the genetic relationship, we followed a series of MR analyses leveraging GWAS summary statistic data. Finally, three sensitivity analyses were involved to further assess the robustness of our findings.

Data were expressed as frequency (percentage) and means $\pm$ standard deviations (SDs) by quintiles of IOP/BP. ANOVA for continuous variables and Chi-square test for categorical variables were used to test the difference across quintiles of IOP/BP.

For observational analysis, the association between IOP/BP and brain volumes was examined using general linear regression models. The equation used for the general linear regression models is: $Y \sim \beta_0 + \beta_{exp} \times X_{exp} + \beta_i \times X_i + \varepsilon$, where Y refers to the brain volume, exp refers to the exposure (IOP/BP), and X_i refers to the corresponding covariate.

We tested four models: 1) unadjusted; 2) adjusted for age and gender, 3) adjusted for Model 2 plus APOE4, education, income, depression, diabetes, alcohol consumption, physical activity, smoking, sleep duration, BMI, HDL-C, LDL-C, and triglycerides; 4) adjusted for Model 3 plus glaucoma, hypertension, and the use of medication for hypertension/glaucoma (IOP and BP were mutually adjusted for). Whether associations between IOP/BP and brain volumes were modified by age, gender, education, APOE4, and systemic hypertension was examined using general linear regression models.

For genetic analysis, two-sample MR analyses were conducted to obtain robust estimates for brain volumes affected by IOP or BP. The MR analysis involved two-stage approaches. The formula for the first stage is: $X \sim \alpha + \gamma \times Z + \varepsilon_x$, where X is the exposure, Z is the IV, γ is the coefficient for the association between the IV and the exposure, and ε_x is the error term. The formula for the second stage is: $Y \sim \beta + \sigma \times \widehat{X} + \varepsilon_Y$, where Y is the outcome, $\widehat{X}$ is the predicted value of the exposure from the first stage, σ is the coefficient for the causal effect of the exposure on the outcome, and ε_Y is the error term. Three assumptions for MR analysis include: 1) The IV is associated with the exposure; 2) The IV is not associated with the known confounders; 3) The IV does not influence the outcome independent of the exposure (Figure S1.).

Inverse-variance weighting (IVW), MR-Egger regression (MR-Egger), and weighted median[39] were performed using MR package in R (version 4.0.3). Sensitivity analyses were performed using MR-Pleiotropy Residual Sum and Outlier method (MR-PRESSO), which detects and excludes SNPs with potential pleiotropic effects.[40] The association between GRS for IOP/BP and brain volumes was also estimated using general linear regression models. The formula for GRS calculation is: $GRS = \sum_{i=1}^{n} \beta_i \times G_i$, where β_i is the effect size for the i-th IV, G_i refers to the number of risk alleles for the i-th IV, and n is the total number of IVs.

Three sets of sensitivity analysis were conducted as complementary analyses. Firstly, given that a large proportion of individuals without MRI data were not included in the analysis, we repeated the observational analysis for the association between IOP/BP and brain volumes using the inverse probability weighting method.[41] Individuals with complete data are weighted by the inverse of their probability of being a complete case in the analysis. Secondly, we conducted a sensitivity analysis to examine the association of GRSs for the IOP or BP with brain volumes. Unlike two-sample MR, which utilizes independent genetic variants as instrumental variables, GRS analysis directly evaluates the cumulative effect size of the aggregated SNPs. The association between genetic predisposition to IOP or BP and brain volume phenotypes was estimated using various linear regression models. These models were adjusted for different covariates, which were utilized in the main analysis. Thirdly, since there is an overlap between the participants in our two-sample MR analysis and those in the GWAS from which we obtained the summary statistics, we used MRlap to correct the bias in IVW for the MR analysis.[42] Lastly, to further rule out the reverse effect, two-sample MR analyses were conducted to test the effect of brain volume phenotypes on IOP/BP.

Missing values for categorical variables were assigned as a single category. Missing values for continuous covariates were assigned as the mean.

Data analyses for the non-MR study were conducted using SAS 9.4 for Windows (SAS Institute Inc.) and all *p* values were two-sided with statistical significance set at <0.05. For multiple comparisons, Benjamin-Hochberg's procedure was used to control the false discovery rate (FDR) at a 5% level.[43]