Associations Between Myopia and Brain Volumes: An Observational and Genetic Analysis

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Purpose. To examine phenotypic and genetic associations between myopia and various brain volumes using the UK Biobank database.

Methods. After 1:1 propensity score matching (PSM) between participants with myopia and healthy controls, the relationship between myopia and brain volumes was examined using general linear regression, with adjustments for covariates including age, sex, ethnicity, Townsend Deprivation Index, lifestyle factors, and disease status. Bonferroni correction was applied for multiple comparisons. Bidirectional Mendelian randomization (MR) and genetic risk score (GRS) were used to assess genetic associations.

Results. After Bonferroni correction, general linear regression revealed that myopia was significantly associated with reduced total brain volume (β, −0.07 mL; 95% confidence interval [CI], −0.11 to −0.03) and white matter volume (β, −0.08 mL; 95% CI, −0.13 to −0.03) in the fully adjusted model. Education significantly modified the myopia–gray matter association, with a stronger negative correlation in individuals without a college education (β, −0.09 mL; 95% CI, −0.15 to −0.04). MR analysis indicated no obvious causal effect of myopia on brain volumes, and GRS analysis revealed only a slight decreasing trend in total brain volume with increasing genetic risk for myopia (P value for trend < 0.05).

Conclusions. Although myopia shows phenotypic associations with brain volumes, including total brain and white matter, and particularly with gray matter in individuals with lower education, genetic analysis (MR and GRS) did not support a causal or genetic link with brain volumes. These findings suggest that residual confounding factors beyond education level may underlie the observed associations between myopia and brain volumes, underscoring the need for further research to elucidate these relationships.

Keywords: myopia, brain volume, phenotypic association, mendelian randomization, genetic risk score

Myopia, also referred to as short-sightedness or nearsightedness, is a significant global health concern that typically develops during childhood and early adulthood.[1] The primary symptom of myopia is blurred vision when viewing distant objects, and it can be corrected with the use of spectacles, contact lenses, or refractive surgery. As myopia progresses due to axial elongation, the risk of myopia-related complications, including retinal detachment, glaucoma, myopic maculopathy, and dense cataract, may lead to visual impairment and blindness.[2,3] Previous studies have suggested that myopia in the elderly is associated with an increased risk of cognitive dysfunction, age-related cataracts, depressive symptoms, and myopic maculopathy.[4–7] By 2050, an estimated 4.9 billion people will be affected by myopia, accounting for 52% of the global population.

Brain volumes are indicators of many neurodegenerative disease.[8] Due to the connection between visual impairment and brain atrophy, the relationship between myopia and brain function is receiving increasing attention. Furthermore, magnetic resonance imaging (MRI) technology has

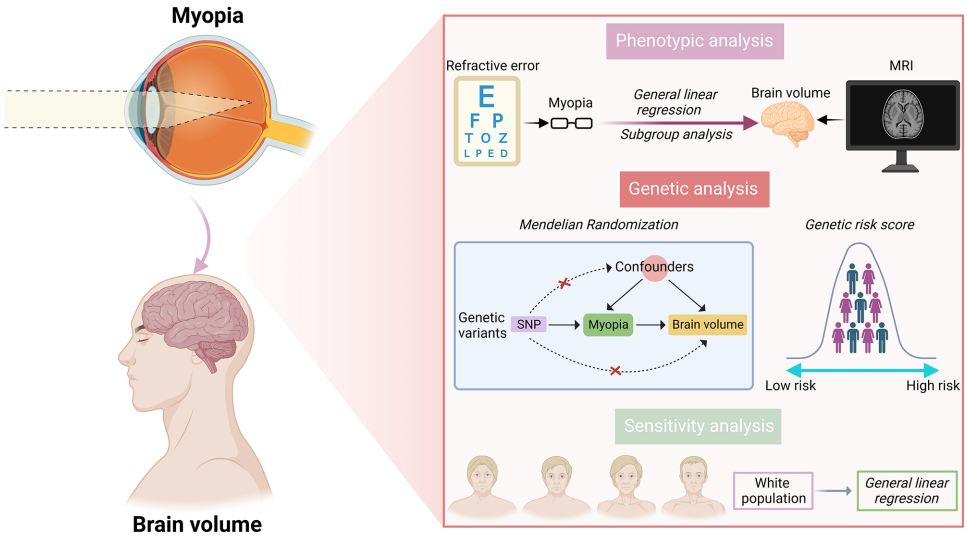

Figure 1. The study explored both phenotypic and genetic associations between myopia and various brain volumes. The phenotypic relationship between myopia and brain volumes was examined using general linear regression and subgroup analysis. The genetic analysis was conducted by bidirectional Mendelian randomization and genetic risk score. The sensitivity analysis was performed in the white population without missing values.

emerged as a powerful tool for studying brain function, allowing the exploration of the association between refractive errors and brain volumes.[9–11] While several studies have investigated the association between high myopia and brain volume, relatively few have investigated the relationship between myopia and brain volume. In a cohort of 1,319 formally educated young adults, Takeuchi et al.[12] found that refractive error was negatively associated with total intracranial volume and total cerebrospinal fluid volume but had no correlation with gray or white matter volumes. For high myopia, some researchers have reported its association with gray matter volume rather than white matter volume.[13–15] However, much of the existing research has focused primarily on young populations, leaving a significant gap in understanding the relationship between prolonged myopia exposure and brain volumes, which neglects the long-term effect of myopia on the brain.

Although the voxel-based morphometry studies have revealed brain changes associated with high myopia, the causal relationship and the genetic basis have not yet been determined. In addition, traditional observational studies face several limitations, including small sample sizes, susceptibility to bias, and a predominant focus on young adult populations.[12–16] Mendelian randomization (MR) applies genetic variants as an instrumental variable (IV), which aims to test a causal hypothesis between the exposure and the outcome. This approach is independent of confounding factors and diminishes the risk of reverse causation bias.[17–19] The genetic risk score (GRS) is a useful tool for evaluating the general genetic contribution or susceptibility to a certain outcome of interest, taking into account the genetic risk alleles.[20] To the best of our knowledge, no previous studies have explored the genetic association and potential causal relationship between myopia and brain volume.

In this study, we sought to examine the correlation between myopia and various brain volumes using the UK Biobank database. Significantly, the analysis employed traditional observational methods, MR and GRS analysis, offering both phenotypic and genetic evidence to support any relationships. Figure 1 presents a schematic overview of the study design.

Methods

Study Population

This study is based on the UK Biobank (https://www.ukbiobank.ac.uk/), a large-scale and prospective cohort study of >500,000 participants aged 40 to 70 years who were recruited between 2006 and 2010. Various phenotypic and genotypic data were gathered from each participant, all of whom provided informed consent through electronic signature. Further details of the UK Biobank data and the associated protocols have been detailed elsewhere.[21] Briefly, a total of 502,505 individuals from 22 assessment centers throughout the United Kingdom participated in this study (a response rate of 5.5%).[21]

The UK Biobank study's ethical approval has previously been granted by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee. This study was conducted under application number 101032 of the Biobank consortium.

Brain MRI

Brain MRI assessment was conducted between 2014 and 2019. All brain imaging scans were obtained using a single, standard Siemens Skyra 3T scanner (Siemens Healthineers, Erlangen, Germany) with a 32-channel radiofrequency receiver head coil.[22] The analysis of T1- and T2-weighted scans was performed by the Functional Magnetic Resonance Imaging of the Brain Software Library. Total brain volume was calculated by the sum of gray matter volume and white matter volume. Volumes of total brain, gray matter, white matter, white matter hyperintensity (WMH), ventricular cerebrospinal fluid, hippocampus, amygdala, and thala-

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mus were normalized for head size, using the ratio-corrected method.[22] To address the positive skewness, we applied a logarithmic transformation to WMH in our analysis.[16,23] All brain volumes were standardized into z-scores for regression analysis using the equation $z = (x - \bar{x})/\sigma$, where x refers to brain volumes, $\bar{x}$ represents mean value of brain volumes, and σ is the standard deviation (SD) of brain volumes.

Definition of Myopia

We calculated the spherical equivalent (SE) using the following formula: sphere + 1/2 cylinder. The mean spherical equivalent (MSE) for both eyes was determined by averaging the SE values of the left and right eyes. Individuals were considered to have myopia if their MSE ≤ -0.75 D, and healthy control was defined by -0.75 D $<$ MSE $<$ 0.75 D.[24] We excluded from the analysis those with preexisting eye conditions that could affect refractive error—namely, cataracts, amblyopia, strabismus, refractive laser eye surgery, corneal graft surgery, or keratorplasty.[24–26]

Covariates

Sociodemographic factors, including age, sex, and ethnic background, were collected through self-report or questionnaire responses. Townsend Deprivation Index was estimated based on residence postcodes. Lifestyle data, including alcohol consumption, smoking status, and qualification information, were obtained using questionnaires on a touchscreen computer. Highest educational qualification was converted to years of education according to the International Standard Classification for Education coding.[27] Educational attainment was categorized as a binary variable for subgroup analysis, distinguishing participants who attended college or university from those with other qualifications.[28] Physical activity levels were assessed as low, moderate, or high using the International Physical Activity Questionnaire (IPAQ). These levels were further classified into above moderate/vigorous/walking exercise recommendations or not, based on metabolic equivalent task scores following IPAQ guidelines.[29] Weight measurements were taken using the Tanita BC-418MA body composition analyzer (Tanita Corporation, Tokyo, Japan), while height was measured with participants in a barefoot standing position using the Saca 202 device. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Hyperlipidemia was identified using a combination of self-report, taking hyperlipidemia-related medications, and blood cholesterol $\geq$6.21 mmol/L.[30,31] Diabetes mellitus was defined by questionnaires, glycated hemoglobin (HbA1c) $\geq$48 mmol/mol, or taking medication for diabetes mellitus.[32] Hypertension was defined as systolic blood pressure $\geq$130 mm Hg, diastolic blood pressure $\geq$80 mm Hg,[33] the use of antihypertensive medications, or self-reported hypertension.

Assessing the Relationship Between Myopia and Brain Volumes

For observational analysis, a general linear regression model was employed to explore the relationship between myopia (exposure) and different brain volumes (outcome). We examined three models: model 1, adjusted for age, sex, ethnicity, and Townsend Deprivation Index; model 2, adjusted for model 1 plus alcohol consumption, smoking status, above moderate/vigorous/walking recommendation or not, BMI, and years of education; and model 3, adjusted for model 2 plus hyperlipidemia, diabetes, and hypertension. Bonferroni correction (0.05/8) was applied to adjust the P values for multiple hypothesis testing, ensuring control over the familywise error rate. In addition, subgroup analysis that took age, sex, and educational attainment into account was utilized to further explore the association between myopia and different brain volumes. Age categorization was defined by $<$55 or $\geq$55 years old, while educational attainment was classified based on whether individuals had attended college or university.

Genotype Data Sources

Two-sample MR analysis: IVs were derived from genome-wide association study (GWAS) summary statistics, and bidirectional MR analyses were performed. In the forward analysis, myopia was considered the exposure, and brain volumes were considered the outcomes. Myopia was initially defined using a combination of MSE ≤ -0.75 D (excluding those with corneal surgeries), hospital health record, questionnaire data (which eyes are affected by myopia and reason for glasses), and myopia surgery, while excluding individuals with cataracts, amblyopia, or strabismus. Controls were defined using -0.75 D $<$ MSE $\leq$ 0.75 D (excluding those with corneal surgeries) or hospital record of myopia diagnosis, also excluding those with cataracts, amblyopia, or strabismus. After excluding individuals with available brain volume measurements, missing genotype data $>$5%, and kinship coefficient $>$0.0884 (third-degree relatives), GWAS for myopia traits was conducted in a sample of 93,242 (28,712 cases and 64,530 controls) unrelated participants of European ancestry from the UK Biobank cohort (Supplementary Figs. S1 and S2). The analysis was performed using PLINK 2.0. A total of 6,556,916 genetic variants were included based on the following quality control criteria: minor allele frequency $\geq$1%, missing genotype call rate $<$5%, Hardy–Weinberg equilibrium $P < 1.0 \times 10^{-6}$, and imputation info score $>$0.8. A logistic model was used to examine the correlation between each single-nucleotide polymorphism (SNP) and individual myopia traits, adjusting for age, sex, and the first 10 ancestry principal components. Genome-wide significant variants ($P < 5 \times 10^{-8}$) were clumped using a 10-Mb window and an linkage disequilibrium threshold of $r^2 < 0.001$, and they were employed as IVs in the MR analysis.[24,34] A total of 42 independent lead SNPs associated with myopia were used as the IV in the forward analysis (Supplementary Table S1). In the forward MR analysis, the SNP-exposure regression coefficients were their effect on myopia from the abovementioned GWAS; the SNP-outcome regression coefficients were derived from GWAS on different brain volumes.

In the reversed analysis, brain volumes were considered the exposures, and myopia was considered the outcome. GWAS was performed for each brain volume trait in a sample of 38,402 unrelated participants of European ancestry in the UK Biobank, following the same GWAS quality control criteria described above. A linear regression model was used to examine the correlation between each SNP and individual brain volume traits, adjusting for age, sex, and the first 10 ancestry principal components. IVs of brain volumes were selected from our GWAS summary statistics following the

same IV selection criteria described above. In total, 20 SNPs for total brain volume, 13 SNPs for gray matter volume, 20 SNPs for white matter volume, and 6 SNPs for amygdala volume were chosen as their IVs, respectively. In the reverse MR analysis, the SNP-exposure coefficients were obtained from our GWAS analysis for brain volume, and SNP-outcome coefficients were obtained from myopia summary statistics mentioned above.

Generation of the GRS

The GRS for myopia was generated based on 42 lead independent SNPs (Supplementary Table S1). GRS for each participant was calculated using the score function implemented in PLINK 2.0.[35] The GRS was derived by summing the SNP allelic dosages, weighted by their corresponding effect sizes (β coefficients):

$$GRS = \sum_{i=1}^{n} \beta_i \times G_i$$

where β_i refers to the effect size for the ith SNP, G_i represents the number of risk alleles for the ith SNP, and n is the total number of SNPs.[36,37]

Statistical Analysis

Data were presented as number (percentage) or mean ± SD, and t-test and Pearson's χ^2 test were used for comparison of continuous variables and categorical variables, respectively, between myopia and healthy control. To reduce selection bias, a 1:1 propensity score matching (PSM) method was applied between myopic and healthy subjects. We employed nearest-neighbor matching with a caliper of 0.1, and the PSM took into account age, sex, and years of education.[38] Subgroup analysis was conducted for age, gender, and education level.

A bidirectional two-sample MR analysis was conducted to evaluate potential causal effects between myopia and brain volumes. The primary method for causal effect estimation was the multiplicative random-effect inverse variance-weighted (IVW) estimate. Sensitivity analysis of MR was performed using MR-Egger regression (MR-Egger), weighted median, weighted mode, simple mode, and MR pleiotropy residual sum and outlier method (MR-PRESSO). All analyses were conducted in the R software version 4.4.1 using the TwoSampleMR package and MR-PRESSO R package.[27,39]

The correlation between GRS for myopia and brain volumes was also conducted using general linear regression models, adjusting for the same covariates as in models 1 to 3 of the phenotypic analysis. To test the nonlinear relationship between GRS for myopia and the brain volumes, we employed restricted cubic splines with 3 knots.[40]

Sensitivity analysis was conducted using general linear regression between myopia and brain volumes in the white population without missing values.

Missing values for categorical covariates were assigned as a separate category, while missing values for continuous covariates were imputed with the mean.

All data analysis was conducted using R 4.4.1 software (R Core Team, Vienna, Austria) or Stata 18 (StataCorp, College Station, TX, USA). All P values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Among the 502,505 participants with baseline data in the UK Biobank study, participants who did not have brain MRI data (n = 464,171) were excluded from the analysis. We further excluded individuals lacking refractive error data (n = 29,392) and those with cataracts, strabismus, amblyopia, or a history of eye surgery (n = 499). This left 8443 participants with refractive error data, who were used to define healthy controls and myopes. Subsequently, 3295 individuals were classified as healthy and 2916 as myopic, resulting in a total of 6211 subjects included in the PSM analysis. Finally, using PSM to balance the myopia and healthy control groups at a 1:1 ratio, 2734 participants with myopia and 2734 healthy participants were included in the study (Fig. 2).

Baseline characteristics between myopes and healthy controls are summarized in Table 1. After PSM, the myopic group showed several differences compared to the healthy control group. Specifically, the myopic group had a lower proportion of smokers (38.84% vs. 33.54%, $P < 0.001$), more patients with diabetes (2.74% vs. 3.73%, $P = 0.039$), and more patients with hypertension (66.86% vs. 70.37%, $P = 0.005$). For brain volumes, the myopic group tended to have less total brain volume, gray matter volume, and white matter volume compared with the healthy control group. Conversely, myopes had more amygdala volume compared to healthy controls.

Phenotypic Association Between Myopia and Different Brain Volumes

We performed three general linear regression models to assess the correlation between myopia and brain volumes (Table 2). In model 1 adjusting for age, sex, ethnicity, and Townsend Deprivation Index, myopia was associated with reduced volumes of total brain (β, −0.07 mL; 95% confidence interval [CI], −0.11 to −0.02), gray matter (β, −0.04 mL; 95% CI, −0.08 to −0.00005), and white matter (β, −0.07 mL; 95% CI, −0.12 to −0.02), as well as an increased volume of the amygdala (β, 0.06 mL; 95% CI, 0.003 to 0.11). With adjustment for more covariates in model 2 and model 3, the association between myopia and gray matter volume became more significant (β, −0.05 mL; 95% CI, −0.09 to −0.01 for model 2; β, −0.04 mL; 95% CI, −0.08 to −0.005 for model 3), whereas the correlation between myopia and amygdala volume was attenuated to be nonsignificant (β, 0.06 mL; 95% CI, 0.002 to 0.11 for model 2; β, 0.05 mL; 95% CI, −0.0004 to 0.11 for model 3). The correlations between myopia and volumes of total brain and white matter remained significant after further adjustment in model 2 and model 3, with βs (95% CIs) for total brain: model 2, −0.07 mL (−0.12 to −0.03) and model 3, −0.07 mL (−0.11 to −0.03); and for white matter: model 2, −0.08 mL (−0.13 to −0.03) and model 3, −0.08 mL (−0.13 to −0.03). However, after adjusting for the multiplicity of hypotheses tested using the Bonferroni correction, the results indicated that myopia was only correlated with volumes of total brain and white matter.

Subgroup Analysis

We further analyzed the interaction effect of age, sex, and education on the association between myopia and brain volumes. The results of the restricted cubic spline analysis

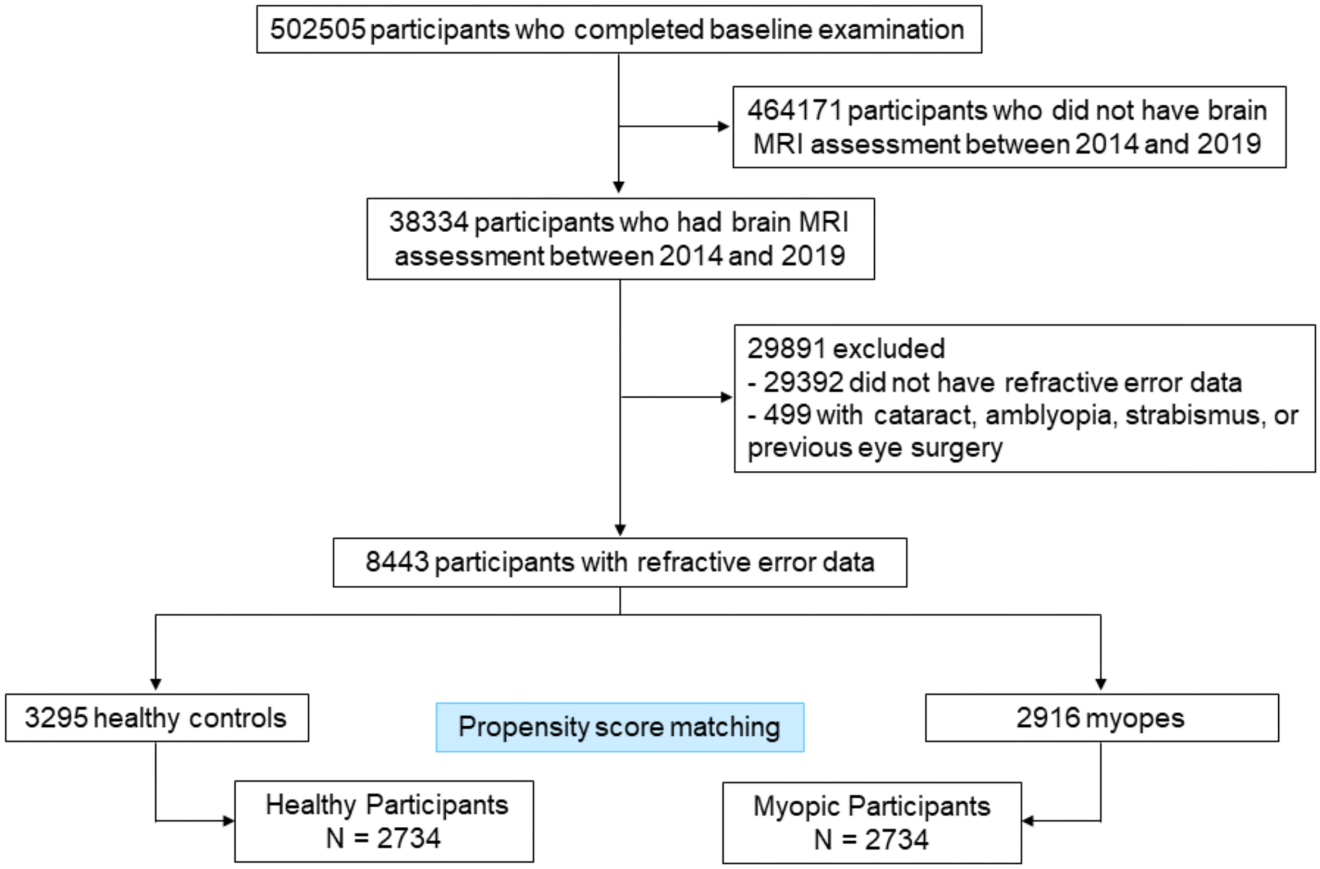

Figure 2. Flowchart depicting population selection from the UK Biobank in this study.

(Supplementary Fig. S3, P for nonlinear = 0.002) indicated a nonlinear relationship between refractive error and age, with approximately 55 years serving as the turning point. Based on this finding, we categorized participants into two age groups: <55 and ≥55. According to the results of subgroup analysis, an interaction effect was observed between myopia and education on gray matter volume (Fig. 3). The negative correlation between myopia and gray matter volume was significant in individuals who did not attend college or university (model 1: β, −0.09 mL; 95% CI, −0.15 to −0.03; model 2: β, −0.10 mL; 95% CI, −0.15 to −0.04; model 3: β, −0.09 mL; 95% CI, −0.15 to −0.04), while there was no correlation between myopia and gray matter volume in participants who attended college or university (model 1: β, 0.01 mL; 95% CI, −0.05 to 0.06; model 2: β, −0.01 mL; 95% CI, −0.06 to 0.05; model 3: β, −0.002 mL; 95% CI, −0.06 to 0.05). No significant interaction effects of age, sex, and education were found for the association between myopia and other brain volumes (Supplementary Figs. S4–S10).

Mendelian Randomization Analysis

We employed a two-sample MR approach to explore bidirectional causal relationships between myopia and volumes of total brain, gray matter, white matter, and amygdala (Table 3 and Supplementary Table S2). To assess the causal effects of myopia on brain volumes, 42 SNPs were applied as IVs (Supplementary Table S1, Supplementary Figs. S1 and S2). The results demonstrated that no statistically significant causal effects of genetically predicted myopia on brain volumes were found in the main IVW analysis, with odds ratios (95% CIs) of 0.97 (0.95–1.00, P = 0.067) for total brain volume, 0.98 (0.95–1.01, P = 0.120) for gray matter volume, 0.98 (0.95–1.01, P = 0.139) for white matter volume, and 50.35 (4.61e−02, 5.50e+04), P = 0.272) for amygdala volume (Table 3). Although the MR-Egger analysis suggested a pleiotropic effect between myopia and gray matter, after correcting the outlier SNPs in MR-PRESSO, the findings remain similar. We further evaluated the effects of brain volumes on myopia. Twenty SNPs for total brain volume, 13 SNPs for gray matter volume, 20 SNPs for white matter volume, and 6 SNPs for amygdala volume were extracted as their IVs. Based on the results, there is no evidence to suggest the casual effects of brain volumes on myopia (Supplementary Table S2).

Genetic Risk Score and Brain Volumes

We divided the GRS for myopia into five quintiles and performed linear correlation analysis between each quintile and brain volumes (Table 4). The results indicated no significant correlations for any quintile (P > 0.05) between GRS for myopia and total brain volume. However, P values for trend across models 1 to 3 were 0.048, 0.046, and 0.046, respectively, indicating a slight decreasing trend in total brain volume as the GRS for myopia increased (Table 4). In model 3, the β coefficients (95% CIs) for the association between GRS for myopia (quintile 2 vs. quintile 1) and brain volumes were as follows: −0.04 mL (−0.07 to −0.005) for ventricular cerebrospinal fluid volume, 0.04 mL (0.002 to 0.07) for the amygdala volume, and 0.04 mL (0.009 to 0.07) for the thalamus volume. Additionally, the β coefficient (95% CI) for

Table 1. Baseline Characteristics and Outcomes of the Study Cohort

Variable	Before PSM			After PSM		
	Healthy Control (n = 3295)	Myopia (n = 2916)	P Value*	Healthy Control (n = 2734)	Myopia (n = 2734)	P Value*
Age, y	53.52 ± 7.44	54.75 ± 7.07	<0.001	54.28 ± 7.25	54.60 ± 7.19	0.112
Sex			0.902			0.808
Male	1595 (48.41)	1407 (48.25)		1312 (47.99)	1321 (48.32)	
Female	1700 (51.59)	1509 (51.75)		1422 (52.01)	1413 (51.68)	
Ethnicity			0.916			0.763
White	3119 (94.66)	2762 (94.72)		2591 (94.77)	2586 (94.59)	
Other	176 (5.34)	154 (5.28)		143 (5.23)	148 (5.41)	
Townsend deprivation index	−1.77 ± 2.71	−1.88 ± 2.65	0.110	−1.77 ± 2.70	−1.87 ± 2.64	0.189
BMI, kg/m^2	26.70 ± 4.22	26.50 ± 4.23	0.063	26.66 ± 4.24	26.53 ± 4.23	0.272
Alcohol consumption			0.168			0.441
Yes	3203 (97.21)	2850 (97.74)		2664 (97.44)	2671 (97.70)	
No	91 (2.76)	63 (2.16)		69 (2.52)	60 (2.19)	
Missing	1 (0.03)	3 (0.10)		1 (0.04)	3 (0.11)	
Smoking status			<0.001			<0.001
Yes	1299 (39.42)	967 (33.16)		1062 (38.84)	917 (33.54)	
No	1988 (60.33)	1944 (66.67)		1666 (60.94)	1812 (66.28)	
Missing	8 (0.24)	5 (0.17)		6 (0.22)	5 (0.18)	
Years of education	15.39 ± 4.70	16.61 ± 4.36	<0.001	16.34 ± 4.41	16.41 ± 4.42	0.560
Above moderate/ vigorous/walking recommendations			0.009			0.088
Yes	2384 (72.35)	2054 (70.44)		1973 (72.17)	1920 (70.23)	
No	478 (14.51)	505 (17.32)		412 (15.07)	472 (17.26)	
Missing	433 (13.14)	357 (12.24)		349 (12.77)	342 (12.51)	
Hyperlipidemia			0.750			0.295
Yes	1309 (39.73)	1170 (40.12)		1126 (41.19)	1088 (39.80)	
No	1986 (60.27)	1746 (59.88)		1608 (58.81)	1646 (60.20)	
Diabetes			0.042			0.039
Yes	92 (2.79)	108 (3.70)		75 (2.74)	102 (3.73)	
No	3203 (97.21)	2808 (96.30)		2659 (97.26)	2632 (96.27)	
Hypertension			0.001			0.005
Yes	2190 (66.46)	2057 (70.54)		1828 (66.86)	1924 (70.37)	
No	1105 (33.54)	859 (29.46)		906 (33.14)	810 (29.63)	
Total brain volume (mL)	1509.01 ± 73.57	1497.55 ± 70.87	<0.001	1504.89 ± 72.90	1498.36 ± 70.89	0.001
Gray matter volume (mL)	801.75 ± 47.95	795.36 ± 45.92	<0.001	799.03 ± 47.52	796.00 ± 45.83	0.017
White matter volume (mL)	707.26 ± 40.55	702.19 ± 40.37	<0.001	705.86 ± 40.45	702.36 ± 40.41	0.001
White matter hyperintensity (mL)	1.14 ± 0.96	1.21 ± 0.97	0.003	1.18 ± 0.95	1.20 ± 0.97	0.414
Ventricular cerebrospinal fluid volume (mL)	43.86 ± 18.92	45.26 ± 19.30	0.004	44.67 ± 19.03	45.08 ± 19.36	0.435
Hippocampus volume (mL)	4.99 ± 0.56	4.99 ± 0.55	0.885	4.98 ± 0.56	4.99 ± 0.55	0.335
Amygdala volume (mL)	1.61 ± 0.26	1.62 ± 0.26	0.079	1.61 ± 0.26	1.62 ± 0.26	0.042
Thalamus volume (mL)	9.97 ± 0.79	9.89 ± 0.80	<0.001	9.94 ± 0.79	9.89 ± 0.80	0.050

Data are mean ± standard deviations (SD) or n (%). BMI, body mass index.
* The t-tests were used to compare continuous variables, while Pearson's χ^2 test was employed to analyze categorical variables between the healthy control group and the myopia group.

amygdala volume associated with GRS for myopia (quintile 4 vs. quintile 1) was 0.04 mL (0.003 to 0.07) in model 3. The restricted cubic spline analysis did not support a nonlinear association between GRS and total brain volume in any of the three models (Supplementary Fig. S11).

Sensitivity Analysis

Sensitivity analysis was conducted in the white ethnicity and those without missing values. As shown in Supplementary Table S3, myopia was negatively correlated with volumes of total brain and white matter after Bonferroni correction. The results of the sensitivity analysis were comparable to the main analysis, indicating the robustness of our findings.

Discussion

In this study, phenotypic analysis demonstrated that myopia was negatively associated with volumes of total brain and white matter after the Bonferroni correction. The phenotypic association between myopia and gray matter volume was stronger in individuals with lower education level. MR analysis did not indicate the obvious casual effects between

Table 2. Association Between Myopia and Different Brain Volumes ($n = 5468$)

Brain Volume (mL)[†]	Model 1[*] Coefficient (95% CI)	*P* Value	Bonferroni-Adjusted *P* Value	Model 2 Coefficient (95% CI)	*P* Value	Bonferroni-Adjusted *P* Value	Model 3 Coefficient (95% CI)	*P* Value[‡]	Bonferroni-Adjusted *P* Value
Total brain	−0.07 (−0.11, −0.02)	0.002	0.019	−0.07 (−0.12, −0.03)	0.001	0.007	−0.07 (−0.11, −0.03)	0.001	0.011
Gray matter	−0.04 (−0.08, −0.00005)	0.050	0.398	−0.05 (−0.09, −0.01)	0.017	0.136	−0.04 (−0.08, −0.005)	0.028	0.224
White matter	−0.07 (−0.12, −0.02)	0.003	0.027	−0.08 (−0.13, −0.03)	0.003	0.024	−0.08 (−0.13, −0.03)	0.003	0.024
White matter hyperintensity	0.003 (−0.04, 0.05)	0.907	1	0.01 (−0.03, 0.06)	0.639	1	0.005 (−0.04, 0.05)	0.845	1
Ventricular cerebrospinal fluid	0.004 (−0.04, 0.05)	0.873	1	0.01 (−0.04, 0.05)	0.751	1	0.01 (−0.04, 0.05)	0.820	1
Hippocampus	0.04 (−0.01, 0.08)	0.140	1	0.03 (−0.01, 0.08)	0.169	1	0.03 (−0.01, 0.08)	0.165	1
Amygdala	0.06 (0.003, 0.11)	0.039	0.315	0.06 (0.002, 0.11)	0.041	0.326	0.05 (−0.0004, 0.11)	0.052	0.414
Thalamus	−0.03 (−0.08, 0.01)	0.131	1	−0.04 (−0.09, 0.004)	0.075	0.600	−0.04 (−0.08, 0.01)	0.090	0.720

[*] Model 1 was adjusted for age, sex, ethnicity, and Townsend Deprivation Index; model 2 was adjusted for model 1 plus alcohol consumption, smoking status, at or above moderate/vigorous/walking recommendations, body mass index, and years of education; model 3 was adjusted for model 2 plus hyperlipidemia, diabetes, and hypertension.

[†] All brain volumes were standardized into *z*-scores.

[‡] General linear regression models were used to analyze the association between myopia and different brain volumes.

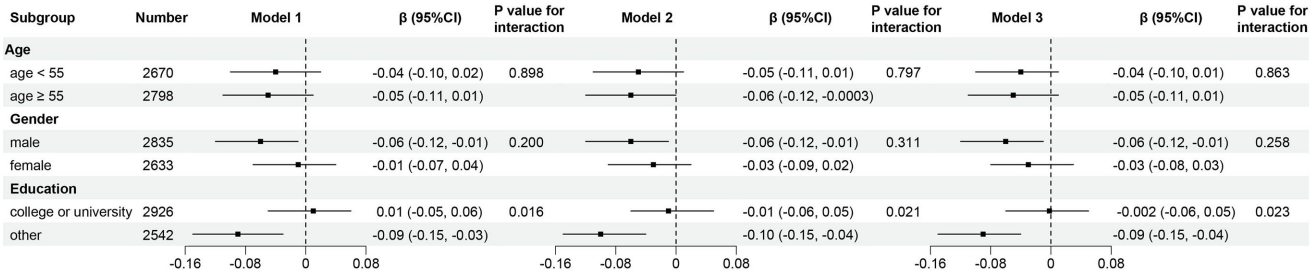

Figure 3. Subgroup analysis for the correlation between myopia and gray matter volume. General linear regression models were employed to assess the interaction effects of myopia with age, sex, and education on gray matter volume. Model 1 was adjusted for age, sex, ethnicity, and Townsend Deprivation Index; model 2 was adjusted for model 1 plus alcohol consumption, smoking status, at or above moderate/vigorous/walking recommendations, body mass index, and years of education; model 3 was adjusted for model 2 plus hyperlipidemia, diabetes, and hypertension. *Horizontal lines* represent the ranges of the 95% CIs, and the *vertical dashed lines* represent the mean of 0.0.

myopia and brain volumes, and GRS results only revealed a slight decreasing trend in total brain volume as the GRS for myopia increases. Finally, the sensitivity analysis in the white population without missing values indicated the robustness of our findings.

In recent years, more and more studies have explored the phenotypic associations between eye health and brain development. Some studies have reported the associations between myopia and white matter. The research by Wang et al.[41,42] demonstrated that high myopia is associated with disrupted white matter microstructure and network organization, characterized by decreased kurtosis metrics (axial, radial, and mean), lower fractional anisotropy, elevated axial diffusivity, and reduced local specialization. This observation is in line with our findings, supporting the notion that myopia is associated with compromised white matter integrity. A voxel-based analysis by Li et al.[43] reported increased concentration of white matter in patients with high myopia, primarily in the calcarine area. Notably, their participants were young adults with an average age of approximately 20 years. Such early-onset high myopia may entail compensatory enhancement of neural connectivity, possibly accounting for the differences observed between their findings and ours. Takeuchi et al.[12] found that the refractive error is negatively correlated with total cerebrospinal fluid volume but not with volumes of gray and white matter. However, they also focused on young adults around 20 years old, a population in whom white matter dysfunction may not lead to structural changes in brain volume due to compensatory mechanisms. Moreover, some studies have reported an association between other ocular diseases and white matter alterations. For example, Liu et al.[44] discovered that abnormal spontaneous alterations in white matter were found in patients with monocular blindness. White matter degeneration within the visual pathways has also been reported in patients with glaucoma.[45,46] Similarly, a study by Allen et al.[47] observed abnormalities in retinothalamic white matter in individuals with amblyopia. All these findings might be attributed to the alterations in nerve fibers,[48,49] which could contribute to reduced white matter volume with aging and, consequently, a decrease in total brain volume.

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Table 3. MR Results for a Causal Effect of Myopia on Brain Volumes With Five MR Methods

			MR Analysis		Heterogeneity Test		Pleiotropy Test		
Exposure	Outcome	Method	OR (95% CI)	*P* Value	Q Statistic (*df*)	*P* Value (Q)	*β* (SE)	*P* Value	No. of SNPs
Myopia	Total brain volume	MR-Egger	1.04 (0.97, 1.12)	0.260	53.48 (40)	0.075	−0.007 (0.003)	0.051	42
		Weighted median	0.98 (0.95, 1.02)	0.322					42
		IVW	0.97 (0.95, 1.00)	0.067	58.90 (41)	0.035			42
		Simple mode	0.98 (0.91, 1.04)	0.491					42
		Weighted mode	0.98 (0.94, 1.03)	0.526					42
Myopia	Gray matter volume	MR-Egger	1.05 (0.98, 1.12)	0.200	59.61 (40)	0.024	−0.007 (0.003)	0.045	42
		Weighted median	0.99 (0.96, 1.02)	0.415					42
		IVW	0.98 (0.95, 1.01)	0.120	66.01 (41)	0.008			42
		Simple mode	0.98 (0.92, 1.05)	0.575					42
		Weighted mode	0.99 (0.95, 1.04)	0.774					42
Myopia	White matter volume	MR-Egger	1.02 (0.95, 1.10)	0.597	44.89 (40)	0.274	−0.004 (0.003)	0.242	42
		Weighted median	0.98 (0.94, 1.02)	0.348					42
		IVW	0.98 (0.95, 1.01)	0.139	46.47 (41)	0.257			42
		Simple mode	0.97 (0.90, 1.04)	0.399					42
		Weighted mode	0.98 (0.93, 1.04)	0.526					42
Myopia	Amygdala volume	MR-Egger	9.52e−02 (8.30e−10, 1.09e+07)	0.805	52.65 (40)	0.087	0.625 (0.873)	0.478	42
		Weighted median	43.10 (3.15e−03, 5.91e+05)	0.439					42
		IVW	50.35 (4.61e−02, 5.50e+04)	0.272	53.33 (41)	0.094			42
		Simple mode	7.05e+07 (0.26, 1.93e+16)	0.076					42
		Weighted mode	1.98 (2.63e+06, 1.50e+06)	0.922					42

Notably, some studies have reported the associations between myopia and gray matter. A voxel-based morphometry study by Huang et al.[13] found that patients with high myopia showed significantly decreased gray matter volumes in the right cuneus/lingual gyrus and the right thalamus. In contrast, they showed larger gray matter volumes in the brainstem, right parahippocampal gyrus/thalamus, left parahippocampal gyrus/thalamus, and the right and left putamen. Similarly, the research by Wu et al.[14] demonstrated cortical thickness reduction and disconnection in the visual center and visual processing areas, along with increased cortical thickness in the left multimodal integration region in patients with high myopia. There is evidence that visual disorders such as amblyopia, albinism, glaucoma, age-related macular degeneration, and visual field defects affect cortical structures and volumes.[50] Combining previous studies with our results, we speculate that alterations in cortical thickness may be linked to functional and structural changes in the eyes of individuals with myopia. These changes might reflect compensatory mechanisms, neural plasticity, or disruptions in typical brain function due to altered visual input.[14,51] However, in our study, the associations between myopia and gray matter volume did not remain significant after Bonferroni correction, indicating the need for further confirmation. The observed increase in amygdala volume in myopic individuals may reflect compensatory mechanisms, although the association weakened after additional adjustments, suggesting potential confounding or a false positive.

Although we compared our findings with previous studies, two key differences should be noted. First, most prior studies focused on younger populations, whereas our study involved older adults. Second, earlier research primarily examined high myopia, while our study included individuals with myopia more generally. These differences may partly explain the inconsistencies, and further research on brain volume alterations in older adults with myopia is warranted to support our findings.

The subgroup analysis revealed that educational attainment significantly modified the association between myopia and gray matter volume. Specifically, the negative correlation was evident in individuals who did not attend college or university but not in those with higher education. Previous studies revealed that myopia is linked to cognitive performance and duration of education.[2,52] Additionally, education has been reported to have a strong relationship with brain volume,[53,54] and some studies have specifically highlighted the association between education and gray matter volume in older adults.[55,56] So the results of subgroup analysis might underscore the potential role of education or cognitive factors in mediating the relationship between myopia and brain structure. Higher education enhances cognitive reserve and promotes healthier lifestyles, potentially mitigating myopia's impact on gray matter volume. In contrast, lower education levels may increase vulnerability due to fewer resources and opportunities for cognitive engagement.

To our knowledge, this study is the first to investigate the association and causal relationship between myopia and brain volumes using a combination of phenotypic and genetic approaches. The two-sample MR analysis did not reveal causal relationships between myopia and various brain volumes, which was consistent with the study by Ferguson et al.[57] that myopia had no causal relationship with brain disease (dementia) in MR analysis. Furthermore, the GRS results did not reveal significant genetic associations between genetic susceptibility to myopia and total brain volume, gray matter volume, or white matter volume. Several factors may contribute to these null findings. First, the genetic instruments derived from GWAS may lack sufficient statistical power to detect modest causal effects, particularly if the SNPs explain only a small proportion of the variance in myopia. Second, the previously observed phenotypic associations between myopia and brain volumes may have been confounded by unmeasured environmental or behavioral factors, such as screen time, sleep patterns, or early-life exposures, which can influence both traits independently. More evidence is needed to identify the genetic associations between myopia and brain volumes.

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Table 4. Association Between Genetic Risk Score for Myopia and Different Brain Volumes

	Genetic Risk Score (Myopia)					
Brain Volume	**Quintile 1 (n = 6377) [−1.42, −0.26]**	**Quintile 2 (n = 6377) [−0.26, −0.04]**	**Quintile 3 (n = 6376) [−0.04, 0.14]**	**Quintile 4 (n = 6377) [0.14, 0.35]**	**Quintile 5 (n = 6376) [0.35, 1.54]**	***P* Value* for Trend**
Total brain volume (mL)	1494.41 ± 72.52	1495.39 ± 73.04	1493.35 ± 74.39	1494.23 ± 72.25	1493.76 ± 72.72	
β (95% CI), model 1†	Reference	0.02 (−0.008, 0.05)	−0.007 (−0.04, 0.02)	−0.01 (−0.04, 0.02)	−0.02 (−0.05, 0.01)	0.048
β (95% CI), model 2	Reference	0.02 (−0.008, 0.05)	−0.006 (−0.03, 0.02)	−0.009 (−0.04, 0.02)	−0.02 (−0.05, 0.01)	0.046
β (95% CI), model 3	Reference	0.02 (−0.008, 0.05)	−0.006 (−0.03, 0.02)	−0.01 (−0.04, 0.02)	−0.02 (−0.05, 0.01)	0.046
Gray matter volume (mL)	792.68 ± 47.75	792.82 ± 47.69	791.38 ± 48.81	792.36 ± 47.78	792.44 ± 47.80	
β (95% CI), model 1	Reference	0.02 (−0.009, 0.04)	−0.02 (−0.04, 0.01)	−0.01 (−0.04, 0.01)	−0.01 (−0.04, 0.01)	0.071
β (95% CI), model 2	Reference	0.02 (−0.007, 0.04)	−0.02 (−0.04, 0.01)	−0.01 (−0.04, 0.02)	−0.01 (−0.04, 0.01)	0.068
β (95% CI), model 3	Reference	0.02 (−0.007, 0.04)	−0.02 (−0.04, 0.01)	−0.01 (−0.04, 0.02)	−0.01 (−0.04, 0.01)	0.064
White matter volume (mL)	701.73 ± 40.83	702.57 ± 40.74	701.97 ± 40.91	701.87 ± 40.21	701.32 ± 40.52	
β (95% CI), model 1	Reference	0.02 (−0.02, 0.05)	0.007 (−0.03, 0.04)	−0.003 (−0.04, 0.03)	−0.02 (−0.05, 0.02)	0.165
β (95% CI), model 2	Reference	0.02 (−0.02, 0.05)	0.007 (−0.03, 0.04)	−0.005 (−0.04, 0.03)	−0.02 (−0.05, 0.02)	0.160
β (95% CI), model 3	Reference	0.01 (−0.02, 0.05)	0.007 (−0.03, 0.04)	−0.005 (−0.04, 0.03)	−0.02 (−0.05, 0.02)	0.166
White matter hyperintensity volume (mL)	6.36 ± 8.04	6.28 ± 8.01	6.37 ± 7.95	6.27 ± 8.45	6.24 ± 7.84	
β (95% CI), model 1	Reference	−0.02 (−0.05, 0.01)	0.004 (−0.03, 0.03)	−0.02 (−0.05, 0.01)	−0.02 (−0.05, 0.006)	0.142
β (95% CI), model 2	Reference	−0.02 (−0.05, 0.009)	0.005 (−0.03, 0.04)	−0.02 (−0.05, 0.007)	−0.02 (−0.05, 0.006)	0.153
β (95% CI), model 3	Reference	−0.02 (−0.05, 0.009)	0.005 (−0.03, 0.03)	−0.02 (−0.05, 0.007)	−0.02 (−0.05, 0.008)	0.190
Ventricular cerebrospinal fluid volume (mL)	47.03 ± 20.26	46.49 ± 19.43	47.04 ± 20.21	46.82 ± 20.38	46.41 ± 19.69	
β (95% CI), model 1	Reference	−0.04 (−0.07, −0.007)	−0.007 (−0.04, 0.02)	−0.006 (−0.04, 0.02)	−0.02 (−0.06, 0.005)	0.577
β (95% CI), model 2	Reference	−0.04 (−0.07, −0.006)	−0.008 (−0.04, 0.02)	−0.006 (−0.04, 0.02)	−0.03 (−0.06, 0.005)	0.556
β (95% CI), model 3	Reference	−0.04 (−0.07, −0.005)	−0.008 (−0.04, 0.02)	−0.005 (−0.04, 0.03)	−0.03 (−0.06, 0.005)	0.567
Hippocampus volume (mL)	4.96 ± 0.58	4.96 ± 0.56	4.94 ± 0.59	4.96 ± 0.59	4.95 ± 0.57	
β (95% CI), model 1	Reference	0.02 (−0.02, 0.05)	−0.02 (−0.05, 0.01)	−0.002 (−0.03, 0.03)	−0.01 (−0.05, 0.02)	0.214
β (95% CI), model 2	Reference	0.02 (−0.01, 0.05)	−0.02 (−0.05, 0.01)	−0.001 (−0.03, 0.03)	−0.01 (−0.05, 0.02)	0.209
β (95% CI), model 3	Reference	0.02 (−0.01, 0.05)	−0.02 (−0.05, 0.01)	−0.001 (−0.03, 0.03)	−0.01 (−0.05, 0.02)	0.219
Amygdala volume (mL)	1.60 ± 0.26	1.61 ± 0.27	1.60 ± 0.27	1.61 ± 0.27	1.61 ± 0.26	
β (95% CI), model 1	Reference	0.04 (0.002, 0.07)	0.02 (−0.02, 0.05)	0.04 (0.004, 0.07)	0.03 (−0.009, 0.06)	0.172
β (95% CI), model 2	Reference	0.04 (0.002, 0.07)	0.02 (−0.02, 0.05)	0.04 (0.003, 0.07)	0.03 (−0.01, 0.06)	0.189
β (95% CI), model 3	Reference	0.04 (0.002, 0.07)	0.02 (−0.02, 0.05)	0.04 (0.003, 0.07)	0.03 (−0.01, 0.06)	0.189
Thalamus volume (mL)	9.86 ± 0.81	9.88 ± 0.80	9.86 ± 0.82	9.88 ± 0.85	9.87 ± 0.82	
β (95% CI), model 1	Reference	0.04 (0.007, 0.07)	0.01 (−0.02, 0.04)	0.01 (−0.02, 0.04)	0.003 (−0.03, 0.03)	0.600
β (95% CI), model 2	Reference	0.04 (0.009, 0.07)	0.01 (−0.02, 0.04)	0.01 (−0.02, 0.05)	0.002 (−0.03, 0.03)	0.574
β (95% CI), model 3	Reference	0.04 (0.009, 0.07)	0.01 (−0.02, 0.04)	0.01 (−0.02, 0.05)	0.002 (−0.03, 0.03)	0.572

* General linear regression models were used to estimate the association between GRS for myopia and brain volumes.

† Model 1 was adjusted for age, sex, ethnicity, and Townsend Deprivation Index; model 2 was adjusted for model 1 plus alcohol consumption, smoking status, at or above moderate/vigorous/walking recommendations, body mass index, and years of education; model 3 was adjusted for model 2 plus hyperlipidemia, diabetes, and hypertension.

There are still some limitations in our study. First, the genetic instruments used in our MR analysis explain only a small proportion of variance in myopia, potentially reducing power to detect modest causal effects. Second, MRI data were collected from a small UK Biobank subset, limiting the generalizability of our results to the entire population. Third, the study cohort predominantly consists of individuals of European ancestry, restricting applicability to other populations. Lastly, the use of bilateral averages for defining myopia may obscure significant interocular differences, and the absence of stratification by myopia severity further limits the precision of the analysis.

In conclusion, our study explored both phenotypic and genetic relationships between myopia and brain volumes. These findings have important implications for understanding the broader neurodevelopmental impacts of myopia. They highlight the need for early interventions to address modifiable risk factors, such as increased outdoor time and reduced screen use, which may influence both visual and cognitive health.

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