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ARTICLE

Bidirectional Causal Relationship Between Myopia and Neurodegenerative Diseases: Two-Sample Mendelian Randomization Analyses

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Abstract

Aims/Background Myopia is highly prevalent in certain neurodegenerative diseases (NDDs), and both conditions demonstrate genetic susceptibility. This study investigated the potential bidirectional causal relationships between myopia and four NDDs, Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), using Mendelian randomization (MR). We aimed to determine whether myopia contributes to the risk of NDDs and vice versa.

Methods We analyzed data from two independent, large-scale genome-wide association study (GWAS) cohorts on myopia, comprising 212,571 participants in the first cohort (finn-b-H7_MYOPIA) and 95,619 in the second (GCST009521). GWAS summary statistics for the four NDDs, encompassing 589,439 samples, were also incorporated. Bidirectional MR was employed to investigate causal relationships between myopia and each of the four NDDs. The inverse variance-weighted (IVW) method served as the primary analytical approach. Sensitivity analyses, including MR-Egger regression, weighted median, weighted mode, and simple mode, were conducted to assess the robustness of the findings. Horizontal pleiotropy was evaluated using the MR-Egger regression intercept test and the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) global test, while heterogeneity was assessed via Cochran's Q test. Leave-one-out analyses were conducted to evaluate the influence of individual single nucleotide polymorphisms (SNPs). Odds ratios (ORs) with 95% confidence intervals (CIs) were reported, and statistical significance was set at $p < 0.05$.

Results MR analyses identified no evidence of a causal relationship between myopia and refractive error and increased risk of any of the four NDDs (all $p > 0.05$). Similarly, none of the NDDs were associated with an increased risk of myopia or refractive error (all $p > 0.05$). Sensitivity analyses revealed no SNPs with significant influence on the causal associations (all $p > 0.05$), supporting the robustness of the findings.

Conclusion This study provides no evidence of a bidirectional causal relationship between myopia and the four NDDs among individuals of European ancestry. Future research should extend beyond direct causal inference to investigate potential mediating biological mechanisms.

Key words: mendelian randomization analysis; myopia; neurodegenerative diseases; retina; brain

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Introduction

The World Health Organization has identified myopia as a significant global cause of visual impairment. By 2050, it is projected that 49.8% of the global population will be affected by myopia (Holden et al, 2016). Myopia is influenced by both

genetic predisposition and environmental factors (Tedja et al, 2019). While genetic predispositions pose challenges for intervention, current preventive and therapeutic interventions are insufficient to meet clinical needs. Increasing attention is now being directed toward non-genetic contributors to myopia, prompting a shift in the early identification of modifiable risk factors.

Neurodegenerative diseases (NDDs), including Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), may be associated with myopia. For instance, in patients with AD, β-amyloid accumulation in the lens can modify its thickness and curvature, potentially increasing myopia severity (Goldstein et al, 2003). Similarly, data from the North American Research Committee on Multiple Sclerosis indicated a higher prevalence of myopia (51.8%) among MS patients (Salter et al, 2013). Emerging evidence also links myopia to functional and structural alterations in brain regions involved in cognitive function. Population-based studies have identified associations between myopia and global brain atrophy, including hippocampal shrinkage (Garzone et al, 2023), suggesting potential neurodegenerative processes. Furthermore, functional MRI in individuals with high myopia has revealed impairments in brain regions responsible for sensory-motor integration and higher-order cognitive processes (Ji et al, 2022), highlighting the broader neurological implications of myopia.

Visual signals originating from the retina are transmitted through complex neural pathways that connect the eyes and the brain, suggesting a potential bidirectional relationship between ocular and neurological health. The growing field of the eye-brain connection highlights how changes in retinal structure may reflect broader alterations associated with NDDs. Recent studies have reported structural and vascular similarities in both myopia and NDDs, such as thinning of the retinal nerve fibre layer (RNFL) and the ganglion cell-inner plexiform layer (GC-IPL) (McCann et al, 2021; Mutlu et al, 2018), along with blood flow abnormalities (Czakó et al, 2020; Trebbastoni et al, 2017). These findings support the hypothesis of a bidirectional relationship between myopia and NDDs. However, the causal nature of this association remains unclear. This uncertainty largely stems from the inherent limitations of observational studies, which are susceptible to biases from reverse causality, confounding variables, and measurement errors. Therefore, adopting alternative methodological approaches to derive more reliable causal inferences is crucial.

Mendelian randomization (MR) addresses these challenges by incorporating instrumental variables (IVs) from econometrics, using genotypes as IVs to estimate the causal relationship between exposures and outcomes. According to Mendel's law of the random assortment of alleles from parents to offspring during gametogenesis, the association between genetic variants and outcomes is not influenced by postnatal environmental exposures, socioeconomic status, behavioural traits, or other common confounders. Additionally, the temporal direction of causality is logical, offering unique advantages for causal inference of exposure factors. This makes MR a powerful alternative to randomized controlled trials for evaluating causality. However, MR studies examining the relationship between myopia and NDDs remain limited.

This study employed two independent, large-scale genome-wide association study (GWAS) datasets on myopia to investigate the potential bidirectional causal relationship between myopia and each of the four NDDs. The study aimed to provide insights into the potential role of the eye-brain connection in these associations while leveraging genetic data to strengthen the robustness of the findings.

Methods

MR Analysis

A bidirectional MR analysis was conducted to establish a conceptual framework (Fig. 1), leveraging genetic variability to investigate potential causal relationships between myopia and four distinct NDDs (PD, AD, MS, and ALS).

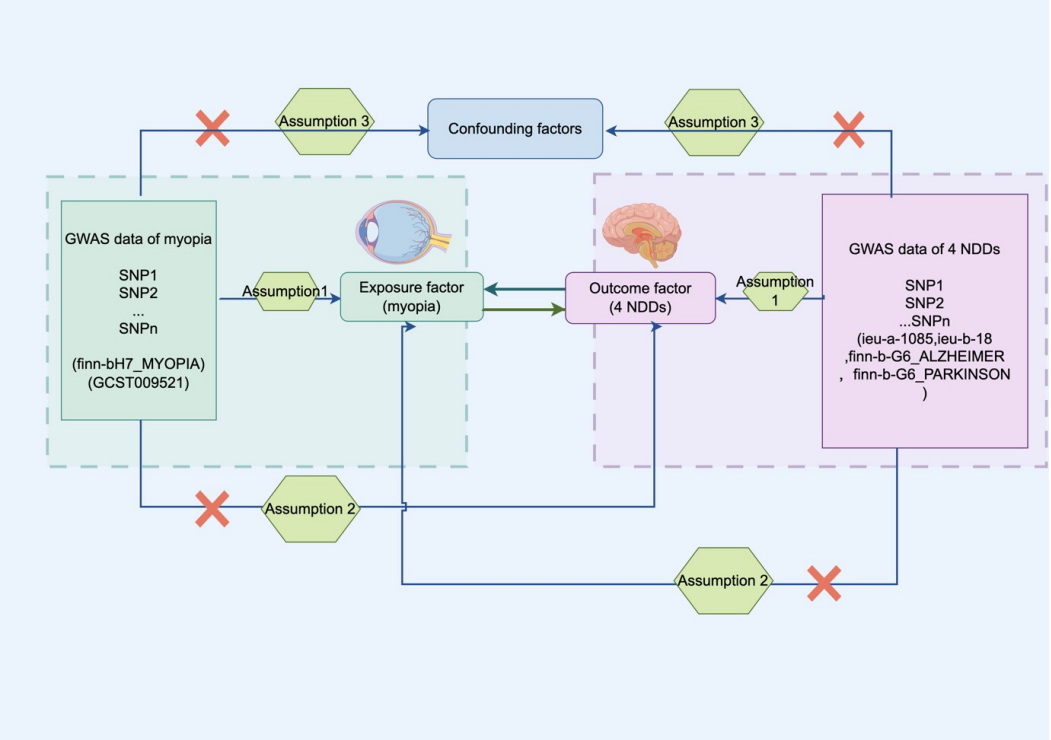

Fig. 1. Conceptual diagram of Mendelian randomization assessing the association between myopia and four neurodegenerative diseases. The diagram illustrates the three core assumptions of Mendelian randomization: (1) the observed genotype must be associated with the exposure factor; (2) the observed genotype can only be related to outcomes when exposure is altered; and (3) the observed genotype must not be affected by confounders (Figure created with Figdraw: https://www.figdraw.com). GWAS, genome-wide association study; SNP, single nucleotide polymorphism; NDDs, neurodegenerative diseases.

Data Source

Data Sets

Relevant datasets were retrieved from two primary sources: The Medical Research Council Integrative Epidemiology Unit (IEU) Open GWAS database (http://gwas.mrcieu.ac.uk/) and FinnGen (https://www.finngen.fi/fi). The specific datasets

Table 1. A summary of GWAS datasets and phenotypic information.

Data source	Phenotype	Sample size	Cases	Population
IEU OpenGWAS project (ieu-a-1085)	Amyotrophic lateral sclerosis (ALS)	36,052	12,577	European
IEU OpenGWAS project (ieu-b-18)	Multiple sclerosis (MS)	115,803	47,429	European
IEU OpenGWAS project (finn-b-G6_PARKINSON)	Parkinson's disease (PD)	218,792	2162	European
IEU OpenGWAS project (finn-b-G6_ALZHEIMER)	Alzheimer's disease (AD)	218,792	3899	European
GWAS Catalog (GCST009521)	Refractive error	95,619	—	European
IEU OpenGWAS project (finn-b-H7_MYOPIA)	Myopia	212,571	1640	European

Abbreviations: IEU, Integrative Epidemiology Unit; GWAS, genome-wide association study.

included ALS (ieu-a-1085), MS (ieu-b-18), AD (finn-b-G6_ALZHEIMER), PD (finn-b-G6_PARKINSON), and two myopia-related datasets: finn-b-H7_MYOPIA and GCST009521. The finn-b-H7_MYOPIA and GCST009521 datasets were selected as genetic instruments for myopia based on the following criteria: (1) both datasets originate from large-scale European cohorts (Finnish cohort: n = 212,571 and UK Biobank: n = 95,619), providing adequate statistical power while minimizing population stratification bias due to independent sampling; (2) these datasets have undergone rigorous quality control and have been widely validated in previous genome-wide association studies (GWAS) on myopia; (3) the cohorts employ distinct phenotypic definitions: finn-b-H7_MYOPIA uses international classification of diseases (ICD)-10/8 diagnostic codes, while GCST009521 defines myopia based on refractive error measured using an automatic ophthalmometer. This phenotypic heterogeneity enhances the robustness of our genetic instruments.

All individuals included in the datasets were of European ancestry. A summary of sample sizes and population characteristics is provided in Table 1. The GWAS summary statistics are publicly available at the following links: ALS (ieu-a-1085): https://gwas.mrcieu.ac.uk/datasets/ieu-a-1085/; MS (ieu-b-18): https://gwas.mrcieu.ac.uk/datasets/ieu-b-18/; PD (finn-b-G6_PARKINSON): https://gwas.mrcieu.ac.uk/datasets/finn-b-G6_PARKINSON/; AD (finn-b-G6_ALZHEIMER): https://gwas.mrcieu.ac.uk/datasets/finn-b-G6_ALZHEIMER/; Myopia (finn-b-H7_MYOPIA): https://gwas.mrcieu.ac.uk/datasets/finn-b-H7_MYOPIA/; refractive error (GCST009521): https://www.ebi.ac.uk/gwas/studies/GCST009521.

Analysis Design

In the first analysis, the finn-b-H7_MYOPIA dataset was used as a genetic proxy for myopia to examine its associations with NDDs, using outcome data from the Medical Research Council Integrative Epidemiology Unit (MRC IEU) Open GWAS and FinnGen databases. In the second analysis, the GCST009521 dataset, defining refractive error based on automated refractometer measurements, was used

to assess relationships with the same four NDDs. Data normalization was performed as necessary to ensure comparability between the two datasets.

Ethical Considerations

Instrument Selection and Assumption Assessment

Instrumental variables (IVs) were selected following the three fundamental assumptions of MR analysis. Single nucleotide polymorphisms (SNPs) associated with NDDs were identified using GWAS summary statistics, applying a significance threshold of $p < 5 \times 10^{-5}$, linkage disequilibrium (LD) criterion of $R^2 > 0.001$, and an LD window of $\leq$10,000 kb. To minimize confounding, SNPs associated with known confounders were excluded using PhenoScanner (https://doi.org/10.1093/bioinformatics/btz469, Accessed: 30 August 2023). Similarly, SNPs associated with myopia or refractive error were filtered using the same significance threshold, with an LD pruning at $R^2 > 0.8$ to retain independent SNPs directly related to myopia. The strength of each IV was evaluated using the F statistic from the first-stage regression, and SNPs with an F statistic $<$10 were excluded to minimize weak instrument bias and satisfy the relevance assumption. To ensure the exclusivity assumption, horizontal pleiotropy was evaluated using two complementary approaches: MR-Egger regression intercept test ($p > 0.05$), where a non-significant intercept indicates no evidence of directional pleiotropy; MR-PRESSO global test ($p > 0.05$), which further detects and corrects for outliers suggestive of horizontal pleiotropy. For the independence assumption, since SNPs are randomly inherited from parents following Mendelian principles, their distribution is theoretically independent of environmental and socioeconomic factors. This minimizes confounding bias and ensures that the genetic instruments are not influenced by unmeasured confounders.

Statistical Analyses

Five MR models were employed to estimate bidirectional causal relationships between myopia and four NDDs (ALS, AD, PD, and MS). Primary causal estimates were derived from the inverse variance-weighted (IVW) method, which offers the most statistically efficient effect estimates under the assumption that all instrumental variables (SNPs) are valid. However, its accuracy depends on the three key MR assumptions: (1) relevance, a strong association between instrumental variables and the exposure; (2) exclusion restriction, instrumental variables affect the outcome only through the exposure; and (3) independence, instrumental variables are independent of confounders. To test the robustness of our findings, four additional MR approaches were employed for sensitivity analysis: MR-Egger regression, weighted median estimator (WME), weighted mode, and simple mode. All analyses were conducted using the Two-SampleMR package (https://github.com/MRCIEU/TwoSampleMR) (Minelli et al, 2021) in R (version 4.2.2; R Core Team, Vienna, Austria).

Sensitivity analyses were performed to detect potential violations of MR assumptions and confirm the robustness of the results. These included MR-Egger regression, leave-one-out tests, and funnel plot asymmetry assessment, where indi-

vidual SNP effect estimates (β or OR) were plotted against their inverse standard errors. MR-Egger regression accounts for potential horizontal pleiotropy by including an intercept term. Additionally, the MR-PRESSO global test was used to detect and correct for potential horizontal pleiotropy, with a non-significant result ($p > 0.05$) indicating no evidence of pleiotropic distortion. Heterogeneity across instrumental SNPs was evaluated using Cochran's Q test, and results from the random-effects IVW model were prioritized when heterogeneity was present. I^2 statistics were calculated to quantify heterogeneity, with values above 50% indicating moderate to high heterogeneity. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated to express the causal effects. For additional sensitivity analysis, a leave-one-out analysis was conducted by sequentially excluding each SNP to evaluate its influence on the overall causal estimate. Statistical significance was defined as a two-tailed p-value < 0.05.

Results

SNP Instrumental Variables (IVs)

Following quality control and screening, the dataset evaluating NDDs as exposures and myopia as the outcome included 221 SNPs (**Supplementary Table 1**). The F-statistics for individual SNPs ranged from 19.5191 to 1269.237 (mean = 40.7582), indicating a minimal risk of weak instrument bias in causal inference. In the reverse analysis, where myopia served as the exposure and NDD as the outcome, 69 SNPs were retained (**Supplementary Table 2**). The F-statistics for these SNPs ranged from 19.6497 to 27.7081 (mean = 22.1945), also suggesting a low likelihood of weak instrument bias in the causal relationship.

The analysis used NDDs as exposures and refractive errors as the outcome, and it included 207 SNPs (**Supplementary Table 3**). The F-statistics for individual SNPs ranged from 19.5191 to 1043.6032 (mean = 35.9029), suggesting a minimal chance of bias from weak instruments in the causal relationship. Conversely, the dataset using refractive error as the exposure and NDDs as the outcome consisted of 954 SNPs (**Supplementary Table 4**). The F-statistic for individual SNPs ranged from 19.5541 to 457.6422 (mean = 41.6112), indicating minimal risk of weak instrument bias in the MR estimates.

Causality Detection

Using Alzheimer's disease (finn-b-G6_ALZHEIMER) as the exposure and myopia (finn-b-H7_MYOPIA) as the outcome, the IVW method revealed no statistically significant causal relationship (OR = 0.9823, 95% CI: 0.8699–1.1093, $p = 0.7739$; Fig. 2A, Table 2). Similarly, across all five MR methods (IVW, MR-Egger, weighted median estimator, weighted mode, and simple mode), no significant causal relationships were observed between any of the four NDDs and myopia (finn-b-H7_MYOPIA) (Table 2). The corresponding MR forest plots (Fig. 2A) visually confirmed the lack of associations, with odd ratios (ORs) consistently close to 1, indicating negligible effect sizes.

In the bidirectional MR analysis, where myopia was used as the exposure and NDDs as the outcomes, no significant causal effects were observed, with OR values consistently close to 1 (Fig. 2B and Table 3). Additionally, none of the five MR approaches (MR-Egger regression, IVW, WME, weighted model, and simple models) yielded statistically significant outcomes (all $p > 0.05$). The direction of the causal effect estimates remained consistent across the five methods. These findings indicate that there is insufficient genetic evidence to support a causal relationship between myopia and any of the four NDDs.

Similarly, MR analyses revealed no significant causal associations between refractive error (GCST009521) and the risk of developing any of the four NDDs (Fig. 3; Tables 4,5). OR estimates derived using the IVW method remained close to 1, suggesting that refractive error does not substantially influence the likelihood of NDD onset. Consistent null results were also observed in the reverse causality analyses, where NDDs were considered as exposures and refractive errors as the outcome, with OR values close to 1 across all MR methods (all $p > 0.05$).

Heterogeneity and Sensitivity Analysis

Heterogeneity tests and sensitivity analyses were conducted for all exposure-outcome pairs to assess the robustness of the MR results. Using AD (finn-b-G6_ALZHEIMER) as the exposure and myopia (finn-b-H7_MYOPIA) as the outcome as an illustrative example, the IVW analysis revealed no significant heterogeneity among the SNPs associated with AD and myopia ($I^2 = 0\%$, Cochran's $Q = 11.5300$, $p = 0.9313$). Scatter and funnel plots demonstrated a symmetrical distribution of SNPs (Fig. 4A,B). The MR-Egger regression intercept was not significantly different from zero ($p = 0.4330$), and MR-PRESSO did not detect significant horizontal pleiotropy effects ($p = 0.9351$), suggesting that the SNPs used in the analysis do not exhibit horizontal pleiotropic effects. Furthermore, leave-one-out analysis confirmed the robustness of the results, as the sequential exclusion of individual SNPs did not disproportionately alter the causal estimates (Fig. 4C).

The same methods were applied to other exposure-outcome combinations (e.g., PD, ALS, and MS with myopia; AD, PD, ALS, and MS with refractive error). Across all pairs, results consistently showed no significant heterogeneity or horizontal pleiotropy, and the sensitivity analyses supported the reliability of the MR findings (**Supplementary Figs. 1–4**).

Discussion

This study employed a bidirectional MR approach using two independent GWAS datasets for myopia, each with distinct phenotypic definitions (ICD-based diagnosis vs. autorefractor-measured refractive error), to comprehensively investigate potential causal relationships with four NDDs. Notably, despite differences in phenotype measurement, both datasets consistently yielded null causal associations (ORs $\approx$ 1.0, 95% CIs spanning unity), suggesting that the findings are robust to phenotypic heterogeneity.

Table 2. Mendelian randomization results for causal links (NDDs as exposure, myopia as outcome).

Outcome	Exposure	N_{SNP}	Methods	MR		Heterogeneity		Horizontal pleiotropy			
				OR (95% CI)	*p*-value	I^2 (%)	Cochran's Q	*p*-value	Egger intercept	SE	*p*-value	MR-PRESSO global test *p*-value
Myopia	Alzheimer's disease	21	MR-Egger	1.1201 (0.7945–1.5792)	0.5251	0	10.8883	0.9275	–0.0264	0.0330	0.4330	0.9351
			Weighted median	0.9076 (0.7678–1.0728)	0.2557	-	-	-	-	-	-	0.9351
			Inverse variance weighted	0.9823 (0.8699–1.1093)	0.7739	0	11.5300	0.9313	-	-	-	0.9351
			Simple mode	0.8483 (0.6232–1.1548)	0.3084	-	-	-	-	-	-	0.9351
			Weighted mode	0.8704 (0.6729–1.1260)	0.3033	-	-	-	-	-	-	0.9351
	Amyotrophic lateral sclerosis	45	MR-Egger	0.5950 (0.1043–3.3928)	0.5619	0	41.2728	0.5464	0.0014	0.0194	0.9429	0.6018
			Weighted median	0.4666 (0.1950–1.1161)	0.0867	-	-	-	-	-	-	0.6018
			Inverse variance weighted	0.6317 (0.3426–1.1649)	0.1413	0	41.2780	0.5890	-	-	-	0.6018
			Simple mode	0.3666 (0.0557–2.4112)	0.3021	-	-	-	-	-	-	0.6018
			Weighted mode	0.3330 (0.0615–1.8044)	0.2089	-	-	-	-	-	-	0.6018
	Multiple sclerosis	138	MR-Egger	1.0113 (0.9339–1.0950)	0.7827	0	128.1672	0.6714	0.0023	0.0060	0.7042	0.6896
			Weighted median	0.9799 (0.9001–1.0667)	0.6388	-	-	-	-	-	-	0.6896
			Inverse variance weighted	1.0239 (0.9764–1.0737)	0.3303	0	128.3120	0.6900	-	-	-	0.6896
			Simple mode	1.0442 (0.8811–1.2374)	0.6187	-	-	-	-	-	-	0.6896
			Weighted mode	0.9918 (0.9042–1.0880)	0.8623	-	-	-	-	-	-	0.6896
	Parkinson's disease	17	MR-Egger	1.0606 (0.8002–1.4056)	0.6882	0	7.7349	0.9340	–0.0005	0.0340	0.9891	0.9564
			Weighted median	1.0807 (0.9290–1.2573)	0.3145	-	-	-	-	-	-	0.9564
			Inverse variance weighted	1.0586 (0.9458–1.1850)	0.3218	0	7.7351	0.9564	-	-	-	0.9564
			Simple mode	1.1465 (0.8746–1.5030)	0.3370	-	-	-	-	-	-	0.9564
			Weighted mode	1.1443 (0.8715–1.5025)	0.3464	-	-	-	-	-	-	0.9564

Abbreviations: CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; SE, standard error of β; SNP, single-nucleotide polymorphism; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

Table 3. Mendelian randomization results for causal links (myopia as exposure, NDDs as outcome).

Outcome	Exposure	N_{SNP}	Methods	MR		Heterogeneity			Horizontal pleiotropy			
				OR (95% CI)	*p*-value	I^2 (%)	Cochran's Q	*p*-value	Egger intercept	SE	*p*-value	MR-PRESSO global test *p*-value
Alzheimer's disease	Myopia	20	MR-Egger	1.0270 (0.9007–1.1709)	0.6953	0.0000	14.3249	0.7077	–0.0192	0.0166	0.2606	0.6885
			Weighted median	0.9266 (0.8482–1.0123)	0.0911	-	-	-	-	-	-	0.6885
			Inverse variance weighted	0.9597 (0.9000–1.0233)	0.2088	0.0000	15.6738	0.6789	-	-	-	0.6885
			Simple mode	0.9131 (0.7738–1.0776)	0.2957	-	-	-	-	-	-	0.6885
			Weighted mode	0.9131 (0.7749–1.0761)	0.2917	-	-	-	-	-	-	0.6885
Amyotrophic lateral sclerosis	Myopia	14	MR-Egger	1.0140 (0.9797–1.0495)	0.4428	49.0000	23.7072	0.0223	–0.0029	0.0041	0.4872	0.0344
			Weighted median	1.0000 (0.9854–1.0148)	0.9953	-	-	-	-	-	-	0.0344
			Inverse variance weighted	1.0024 (0.9887–1.0163)	0.7280	47.0000	24.7223	0.0251	-	-	-	0.0344
			Simple mode	0.9978 (0.9725–1.0238)	0.8715	-	-	-	-	-	-	0.0344
			Weighted mode	0.9992 (0.9789–1.0200)	0.9431	-	-	-	-	-	-	0.0344
Multiple sclerosis	Myopia	15	MR-Egger	1.0988 (0.9120–1.3239)	0.3396	18.0000	15.9395	0.2524	–0.0167	0.0199	0.4168	0.2452
			Weighted median	1.0502 (0.9723–1.1343)	0.2133	-	-	-	-	-	-	0.2452
			Inverse variance weighted	1.0188 (0.9608–1.0804)	0.5327	17.0000	16.8021	0.2669	-	-	-	0.2452
			Simple mode	1.0867 (0.9456–1.2488)	0.2609	-	-	-	-	-	-	0.2452
			Weighted mode	1.0944 (0.9634–1.2434)	0.1873	-	-	-	-	-	-	0.2452
Parkinson's disease	Myopia	20	MR-Egger	0.9489 (0.8057–1.1175)	0.5375	0.0000	14.3504	0.7060	–0.0070	0.0206	0.7367	0.7762
			Weighted median	0.9535 (0.8567–1.0612)	0.3833	-	-	-	-	-	-	0.7762
			Inverse variance weighted	0.9256 (0.8544–1.0028)	0.0584	0.0000	14.4669	0.7558	-	-	-	0.7762
			Simple mode	0.9582 (0.8042–1.1417)	0.6381	-	-	-	-	-	-	0.7762
			Weighted mode	0.9561 (0.7968–1.1471)	0.6345	-	-	-	-	-	-	0.7762

Abbreviations: CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; SE, standard error of β; SNP, single-nucleotide polymorphism; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

Table 4. Mendelian randomization results for causal links (NDDs as exposure, refractive error as outcome).

Outcome	Exposure	N_{SNP}	Methods	MR		Heterogeneity			Horizontal pleiotropy		
				OR (95% CI)	*p*-value	I^2 (%)	Cochran's Q	*p*-value	Egger intercept	SE	*p*-value	MR-PRESSO global test *p*-value
Refractive error	Alzheimer's disease	19	MR-Egger	0.9515 (0.8657–1.0457)	0.3163	4	17.6270	0.4127	0.0106	0.0098	0.2944	0.4261
			Weighted median	0.9773 (0.9279–1.0293)	0.3855	-	-	-	-	-	-	0.4261
			Inverse variance weighted	0.9979 (0.9604–1.0370)	0.9156	4	18.8404	0.4017	-	-	-	0.4261
			Simple mode	0.9834 (0.9033–1.0707)	0.7048	-	-	-	-	-	-	0.4261
			Weighted mode	0.9813 (0.9149–1.0525)	0.6039	-	-	-	-	-	-	0.4261
	Amyotrophic lateral sclerosis	46	MR-Egger	0.9086 (0.4913–1.6802)	0.7613	19	54.2051	0.1393	0.0004	0.0070	0.9512	0.1663
			Weighted median	1.0488 (0.7830–1.4050)	0.7492	-	-	-	-	-	-	0.1663
			Inverse variance weighted	0.9251 (0.7485–1.1434)	0.4715	17	54.2097	0.1634	-	-	-	0.1663
			Simple mode	1.1443 (0.6241–2.0981)	0.6650	-	-	-	-	-	-	0.1663
			Weighted mode	1.0902 (0.6759–1.7583)	0.7250	-	-	-	-	-	-	0.1663
	Multiple sclerosis	126	MR-Egger	0.9915 (0.9629–1.0210)	0.5697	19	153.8396	0.0357	–0.0003	0.0022	0.8966	0.0365
			Weighted median	1.0182 (0.9914–1.0458)	0.1845	-	-	-	-	-	-	0.0365
			Inverse variance weighted	0.9900 (0.9727–1.0075)	0.2618	19	153.8607	0.0407	-	-	-	0.0365
			Simple mode	1.0357 (0.9710–1.1048)	0.2887	-	-	-	-	-	-	0.0365
			Weighted mode	1.0218 (0.9869–1.0579)	0.2259	-	-	-	-	-	-	0.0365
	Parkinson's disease	16	MR-Egger	1.0551 (0.9512–1.1703)	0.3281	44	25.0888	0.0337	–0.0046	0.0132	0.7327	0.0545
			Weighted median	1.0240 (0.9720–1.0788)	0.3729	-	-	-	-	-	-	0.0545
			Inverse variance weighted	1.0380 (0.9907–1.0875)	0.1168	41	25.3063	0.0460	-	-	-	0.0545
			Simple mode	1.0353 (0.9430–1.1366)	0.4775	-	-	-	-	-	-	0.0545
			Weighted mode	1.0162 (0.9251–1.1163)	0.7423	-	-	-	-	-	-	0.0545

Abbreviations: CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; SE, standard error of β; SNP, single-nucleotide polymorphism; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

Table 5. Mendelian randomization results for causal links (refractive error as exposure, NDDs as outcome).

Outcome	Exposure	N_{SNP}	Methods	MR		Heterogeneity			Horizontal pleiotropy			
				OR (95% CI)	*p*-value	I^2 (%)	Cochran's Q	*p*-value	Egger intercept	SE	*p*-value	MR-PRESSO global test *p*-value
Alzheimer disease	Refractive error	254	MR-Egger	1.1172 (1.0039–1.2433)	0.0432	9.0000	277.3995	0.1303	–0.0084	0.0049	0.0895	0.1155
			Weighted median	1.0637 (0.9931–1.1393)	0.0780	-	-	-	-	-	-	0.1155
			Inverse variance weighted	1.0264 (0.9821–1.0727)	0.2464	10.0000	280.5982	0.1123	-	-	-	0.1155
			Simple mode	1.0891 (0.9061–1.3092)	0.3640	-	-	-	-	-	-	0.1155
			Weighted mode	1.0806 (0.9800–1.1915)	0.1211	-	-	-	-	-	-	0.1155
Amyotrophic lateral sclerosis	Refractive error	239	MR-Egger	1.0022 (0.9863–1.0183)	0.7910	10.0000	262.9639	0.1186	–0.0002	0.0007	0.7745	0.1231
			Weighted median	0.9957 (0.9855–1.0060)	0.4143	-	-	-	-	-	-	0.1231
			Inverse variance weighted	1.0000 (0.9939–1.0062)	0.9983	10.0000	263.0551	0.1270	-	-	-	0.1231
			Simple mode	0.9800 (0.9519–1.0090)	0.1763	-	-	-	-	-	-	0.1231
			Weighted mode	0.9833 (0.9574–1.0098)	0.2158	-	-	-	-	-	-	0.1231
Multiple sclerosis	Refractive error	207	MR-Egger	0.9883 (0.9013–1.0837)	0.8032	27.0000	279.4601	<0.001	0.0019	0.0041	0.6408	<0.001
			Weighted median	1.0283 (0.9752–1.0843)	0.3020	-	-	-	-	-	-	<0.001
			Inverse variance weighted	1.0086 (0.9737–1.0448)	0.6338	26.0000	279.7578	<0.001	-	-	-	<0.001
			Simple mode	1.0180 (0.9070–1.1426)	0.7620	-	-	-	-	-	-	<0.001
			Weighted mode	1.0231 (0.9492–1.1029)	0.5509	-	-	-	-	-	-	<0.001
Parkinson's disease	Refractive error	254	MR-Egger	0.9941 (0.8749–1.1296)	0.9279	1.0000	255.3947	0.4285	–0.0011	0.0059	0.8560	0.4501
			Weighted median	1.0164 (0.9291–1.1119)	0.7226	-	-	-	-	-	-	0.4501
			Inverse variance weighted	0.9834 (0.9332–1.0364)	0.5327	1.0000	255.4281	0.4454	-	-	-	0.4501
			Simple mode	0.9036 (0.7208–1.1328)	0.3804	-	-	-	-	-	-	0.4501
			Weighted mode	1.0597 (0.9265–1.2121)	0.3984	-	-	-	-	-	-	0.4501

Abbreviations: CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; SE, standard error of β; SNP, single-nucleotide polymorphism; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

A

Exposure	Outcome	Nsnp	Methods	OR(95%CI)	P-value	Heterogeneity	Horizontal pleiotropy	MR-PRESSO
Alzheimer's disease	Myopia	21	MR Egger	1.1201(0.7945-1.5792)	0.5251	0.9275	0.4330	0.9351
			Weighted median	0.9076(0.7678-1.0728)	0.2557	NA	NA	0.9351
			Inverse variance weighted	0.9823(0.8699-1.1093)	0.7739	0.9313	NA	0.9351
			Simple mode	0.8483(0.6232-1.1548)	0.3084	NA	NA	0.9351
			Weighted mode	0.8704(0.6729-1.1260)	0.3033	NA	NA	0.9351
Amyotrophic lateral sclerosis		45	MR Egger	0.5950(0.1043-3.3928)	0.5619	0.5464	0.9429	0.6018
			Weighted median	0.4666(0.1950-1.1161)	0.0867	NA	NA	0.6018
			Inverse variance weighted	0.6317(0.3426-1.1649)	0.1413	0.5890	NA	0.6018
			Simple mode	0.3666(0.0557-2.4112)	0.3021	NA	NA	0.6018
			Weighted mode	0.3330(0.0615-1.8044)	0.2089	NA	NA	0.6018
multiple sclerosis		138	MR Egger	1.0113(0.9339-1.0950)	0.7827	0.6714	0.7042	0.6896
			Weighted median	0.9799(0.9001-1.0667)	0.6388	NA	NA	0.6896
			Inverse variance weighted	1.0239(0.9764-1.0737)	0.3303	0.6900	NA	0.6896
			Simple mode	1.0442(0.8811-1.2374)	0.6187	NA	NA	0.6896
			Weighted mode	0.9918(0.9042-1.0880)	0.8623	NA	NA	0.6896
Parkinson's disease		17	MR Egger	1.0606(0.8002-1.4056)	0.6882	0.9340	0.9891	0.9564
			Weighted median	1.0807(0.9290-1.2573)	0.3145	NA	NA	0.9564
			Inverse variance weighted	1.0586(0.9458-1.1850)	0.3218	0.9564	NA	0.9564
			Simple mode	1.1465(0.8746-1.5030)	0.3370	NA	NA	0.9564
			Weighted mode	1.1443(0.8715-1.5025)	0.3464	NA	NA	0.9564

B

Outcome	Exposure	Nsnp	Methods	OR(95%CI)	P-value	Heterogeneity	Horizontal pleiotropy	MR-PRESSO
Alzheimer's disease	Myopia	20	MR Egger	1.0270(0.9007-1.1709)	0.6953	0.7077	0.2606	0.6885
			Weighted median	0.9266(0.8482-1.0123)	0.0911	NA	NA	0.6885
			Inverse variance weighted	0.9597(0.9000-1.0233)	0.2088	0.6789	NA	0.6885
			Simple mode	0.9131(0.7738-1.0776)	0.2957	NA	NA	0.6885
			Weighted mode	0.9131(0.7749-1.0761)	0.2917	NA	NA	0.6885
Amyotrophic lateral sclerosis	Myopia	14	MR Egger	1.0140(0.9797-1.0495)	0.4428	0.0223	0.4872	0.0344
			Weighted median	1.0000(0.9854-1.0148)	0.9953	NA	NA	0.0344
			Inverse variance weighted	1.0024(0.9887-1.0163)	0.7280	0.0251	NA	0.0344
			Simple mode	0.9978(0.9725-1.0238)	0.8715	NA	NA	0.0344
			Weighted mode	0.9992(0.9789-1.0200)	0.9431	NA	NA	0.0344
multiple sclerosis	Myopia	15	MR Egger	1.0988(0.9120-1.3239)	0.3396	0.2524	0.4168	0.2452
			Weighted median	1.0502(0.9723-1.1343)	0.2133	NA	NA	0.2452
			Inverse variance weighted	1.0188(0.9608-1.0804)	0.5327	0.2669	NA	0.2452
			Simple mode	1.0867(0.9456-1.2488)	0.2609	NA	NA	0.2452
			Weighted mode	1.0944(0.9634-1.2434)	0.1873	NA	NA	0.2452
Parkinson's disease	Myopia	20	MR Egger	0.9489(0.8057-1.1175)	0.5375	0.7060	0.7367	0.7762
			Weighted median	0.9535(0.8567-1.0612)	0.3833	NA	NA	0.7762
			Inverse variance weighted	0.9256(0.8544-1.0028)	0.0584	0.7558	NA	0.7762
			Simple mode	0.9582(0.8042-1.1417)	0.6381	NA	NA	0.7762
			Weighted mode	0.9561(0.7968-1.1471)	0.6345	NA	NA	0.7762

Fig. 2. Bidirectional MR forest plots between myopia and neurodegenerative diseases (NDDs). (A) Causal estimates with NDDs as exposures and myopia (finn-b-H7_MYOPIA) as the outcome. (B) Causal estimates with myopia (finn-b-H7_MYOPIA) as the exposure and NDDs as outcomes. Abbreviations: CI, confidence interval; MR, Mendelian randomization; OR, odds ratio.

A

Exposure	Outcome	Nsnp	Methods	OR(95%CI)	P-value	Heterogeneity	Horizontal pleiotropy	MR-PRESSO
Alzheimer's disease	refractive error	19	MR Egger	0.9515(0.8657-1.0457)	0.3163	0.4127	0.2944	0.4261
			Weighted median	0.9773(0.9279-1.0293)	0.3855	NA	NA	0.4261
			Inverse variance weighted	0.9979(0.9604-1.0370)	0.9156	0.4017	NA	0.4261
			Simple mode	0.9834(0.9033-1.0707)	0.7048	NA	NA	0.4261
			Weighted mode	0.9813(0.9149-1.0525)	0.6039	NA	NA	0.4261
Amyotrophic lateral sclerosis		46	MR Egger	0.9086(0.4913-1.6802)	0.7613	0.1393	0.9512	0.1663
			Weighted median	1.0488(0.7830-1.4050)	0.7492	NA	NA	0.1663
			Inverse variance weighted	0.9251(0.7485-1.1434)	0.4715	0.1634	NA	0.1663
			Simple mode	1.1443(0.6241-2.0981)	0.6650	NA	NA	0.1663
			Weighted mode	1.0902(0.6759-1.7583)	0.7250	NA	NA	0.1663
multiple sclerosis		126	MR Egger	0.9915(0.9629-1.0210)	0.5697	0.0357	0.8966	0.0365
			Weighted median	1.0182(0.9914-1.0458)	0.1845	NA	NA	0.0365
			Inverse variance weighted	0.9900(0.9727-1.0075)	0.2618	0.0407	NA	0.0365
			Simple mode	1.0357(0.9710-1.1048)	0.2887	NA	NA	0.0365
			Weighted mode	1.0218(0.9869-1.0579)	0.2259	NA	NA	0.0365
Parkinson's disease		16	MR Egger	1.0551(0.9512-1.1703)	0.3281	0.0337	0.7327	0.0545
			Weighted median	1.0240(0.9720-1.0788)	0.3729	NA	NA	0.0545
			Inverse variance weighted	1.0380(0.9907-1.0875)	0.1168	0.0460	NA	0.0545
			Simple mode	1.0353(0.9430-1.1366)	0.4775	NA	NA	0.0545
			Weighted mode	1.0162(0.9251-1.1163)	0.7423	NA	NA	0.0545

B

Outcome	Exposure	Nsnp	Methods	OR(95%CI)	P-value	Heterogeneity	Horizontal pleiotropy	MR-PRESSO
Alzheimer's disease	refractive error	254	MR Egger	1.1172(1.0039-1.2433)	0.0432	0.1303	0.0895	0.1155
			Weighted median	1.0637(0.9931-1.1393)	0.0780	NA	NA	0.1155
			Inverse variance weighted	1.0264(0.9821-1.0727)	0.2464	0.1123	NA	0.1155
			Simple mode	1.0891(0.9061-1.3092)	0.3640	NA	NA	0.1155
			Weighted mode	1.0806(0.9800-1.1915)	0.1211	NA	NA	0.1155
Amyotrophic lateral sclerosis	refractive error	239	MR Egger	1.0022(0.9863-1.0183)	0.7910	0.1186	0.7745	0.1231
			Weighted median	0.9957(0.9855-1.0060)	0.4143	NA	NA	0.1231
			Inverse variance weighted	1.0000(0.9939-1.0062)	0.9983	0.1270	NA	0.1231
			Simple mode	0.9800(0.9519-1.0090)	0.1763	NA	NA	0.1231
			Weighted mode	0.9833(0.9574-1.0098)	0.2158	NA	NA	0.1231
multiple sclerosis	refractive error	207	MR Egger	0.9883(0.9013-1.0837)	0.8032	<0.001	0.6408	<0.001
			Weighted median	1.0283(0.9752-1.0843)	0.3020	NA	NA	<0.001
			Inverse variance weighted	1.0086(0.9737-1.0448)	0.6338	<0.001	NA	<0.001
			Simple mode	1.0180(0.9070-1.1426)	0.7620	NA	NA	<0.001
			Weighted mode	1.0231(0.9492-1.1029)	0.5509	NA	NA	<0.001
Parkinson's disease	refractive error	254	MR Egger	0.9941(0.8749-1.1296)	0.9279	0.4285	0.8560	0.4501
			Weighted median	1.0164(0.9291-1.1119)	0.7226	NA	NA	0.4501
			Inverse variance weighted	0.9834(0.9332-1.0364)	0.5327	0.4454	NA	0.4501
			Simple mode	0.9036(0.7208-1.1328)	0.3804	NA	NA	0.4501
			Weighted mode	1.0597(0.9265-1.2121)	0.3984	NA	NA	0.4501

Fig. 3. Bidirectional MR forest plots between refractive error and neurodegenerative diseases (NDDs). (A) Causal effect estimates of the NDDs as exposures and refractive error (GCST009521) as the outcome. (B) Causal effect estimates of refractive error (GCST009521) as the exposure and the NDDs as outcomes. Abbreviations: CI, confidence interval; MR, Mendelian randomization; OR, odds ratio.

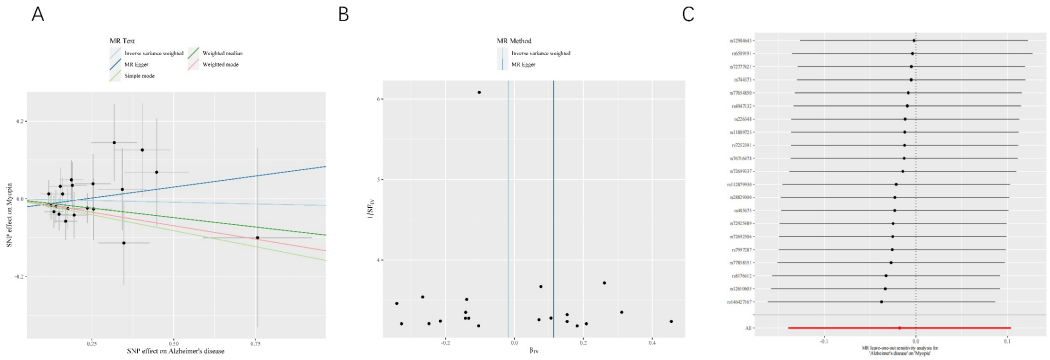

Fig. 4. Heterogeneity and pleiotropy tests for the association between Alzheimer's disease (exposure) and myopia (outcome). (A) MR scatter plot, (B) funnel plot assessing heterogeneity, and (C) leave-one-out sensitivity analysis. Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism.

These findings align with previous observational studies reporting no increased risk of NDDs among individuals with myopia. For instance, a 48-year longitudinal cohort study identified no association between late-adolescent myopia and subsequent development of MS (Hiyoshi et al, 2023). Similarly, a recent study by Ferguson et al (2024), which employed a bidirectional MR approach, reported no significant genetic association between myopia and dementia. Their observational analysis likewise failed to support a positive association (hazard ratio = 0.92), reinforcing the consistency of null findings across different study designs.

In contrast, large population-based studies have reported associations between myopia and cognitive function. A cohort of over one million Israeli adolescents revealed that individuals with higher cognitive scores were more likely to present myopia, especially high myopia (OR = 1.85–2.73), while those with lower cognitive scores had reduced myopia risk (OR = 0.59) (Megreli et al, 2020). Similarly, in the Singapore Malay population, myopia was positively associated with cognitive impairment (OR = 1.82) (Ong et al, 2013). Although these observational findings suggest a possible link, our MR results indicate no genetic causal relationship. This highlights the necessity of exploring non-genetic mechanisms, such as neuroinflammation and neurotransmitter dysregulation, to better understand the eye-brain connection. Notably, overlapping features such as neuroinflammation, neurotransmitter dysregulation, and retinal structural alterations, implicated in both myopia and NDDs, may represent parallel downstream processes rather than direct causal links at the genetic level.

Neuroinflammation is a shared biological mechanism that has been implicated in both myopia and NDDs. It is characterized by the activation of microglia, which plays a crucial role in mediating neurodegenerative alterations. Microglial activation can trigger neuroinflammatory responses that contribute to retinal thinning. In AD and PD, activated microglia are observed in the retina and brain, exhibiting similar transcriptional signatures despite regional variability (Li et al, 2019). In patients with AD, increased microglial activation and retinal ganglion cell (RGC) axonal degeneration have been documented in the retina (Xu et al, 2022). In patients with PD, Toll-like receptor 2-mediated microglial activation induces neuroinflammation and

retinal thinning (Song et al, 2021). In MS, early microglial activation contributes to neurodegeneration and thinning of the inner nuclear layer (INL). Additionally, in ALS, p62-positive inclusions in bipolar and photoreceptor cells of the INL may contribute to neurotoxicity, axonal degeneration, and INL thinning (Fawzi et al, 2014).

Similar neurodegenerative changes have been observed in myopia. For example, signal transducer and activator of transcription 3 (STAT3) signaling, associated with neuroinflammation, is upregulated in retinal microglia of highly myopic mice (Yao et al, 2023). Moreover, myopic *Callithrix jacchus* exhibit thinning of the retinal nerve fiber layer (RNFL), accompanied by increased microglial activation and glial fibrillary acidic protein expression in the foveal area (Lin et al, 2022). Collectively, these findings suggest that neuroinflammation may represent a shared biological mechanism underlying both myopia and NDDs, even in the absence of a direct genetic causal link.

Altered neurotransmitter levels significantly affect visual information processing in both the brain and retina, and contribute to myopia development. Research into the pathogenesis of NDDs and myopia has revealed similar alterations in neurotransmitter profiles. For instance, excessive glutamate (Glu) release may lead to excitotoxicity in the brain, a mechanism implicated in ALS, AD, and PD (Bittigau and Ikonomidou, 1997). In transgenic AD model rats, Glu expression is upregulated in the retina, with significant gamma-aminobutyric acid (GABA) staining (Araya-Arriagada et al, 2021). Similarly, in guinea pig models of form-deprivation myopia, the retina exhibits increased Glu and decreased dopamine (DA) and GABA concentrations (Wei et al, 2023). Patients with PD showed reduced DA levels in the brain and retina, contributing to dopaminergic neuronal degeneration (Indrieri et al, 2020).

Modulation of retinal DA levels plays a crucial role in determining susceptibility to experimentally induced form-deprivation myopia in animal models and acts as a signaling mechanism that inhibits myopia progression (Shu et al, 2023). Moreover, GABAergic neurotransmission modulation has been implicated in several neurodegenerative conditions characterized by dysregulated intracellular calcium homeostasis. Altered GABA levels have also been linked to the pathogenesis of myopia (Błaszczyk, 2016). In addition, a previous study has demonstrated a significant reduction in brain-derived neurotrophic factor (BDNF) levels in the aqueous humor of individuals with high myopia (Wang et al, 2021). Given that BDNF is essential for neuronal survival and the maintenance of synaptic plasticity, its downregulation has been linked to the pathogenesis of AD, ALS, and PD (Al-Kuraishy et al, 2024; Lanuza et al, 2019). The BDNF/tropomyosin receptor kinase B (TrkB) signaling pathway is also essential for maintaining the integrity of neuromuscular junctions (Lanuza et al, 2019), further supporting a potential mechanistic link between myopia and neurodegeneration. These parallel changes in neurotransmitter levels across the brain and retina may provide additional explanations for the associations between myopia and NDDs.

The potential overlap in candidate genes and molecular pathways may also provide insights into the bidirectional relationship between myopia and NDDs. No-

tably, the apolipoprotein E (*APOE*) locus, known for its role in chronic central nervous system inflammation, has been linked to both PD and AD (Fernández-Calle et al, 2022). Primary SNPs identified through GWAS for both conditions have shown overlapping candidate genes, primarily those involved in synaptic signaling and neuronal projection development (Arneson et al, 2018). Single-cell RNA sequencing study has revealed *APOE* expression in the retinas of mice exhibiting high myopia (Yao et al, 2023). Moreover, recent GWAS conducted in highly myopic Asian populations have revealed novel genetic loci associated with synaptic signaling and neuronal development, reinforcing the significance of the nervous system in the etiology of high myopia (Meguro et al, 2020). Further investigation using functional genomics and transcriptomics may help elucidate these shared biological pathways.

Additionally, environmental and behavioral factors may play a dual role in the pathogenesis of both myopia and NDDs. Physical activity has been identified as a modifiable factor influencing myopia progression (Ma et al, 2024), while also exhibiting protective effects against neurodegeneration (Zheng et al, 2024). This underscores the intertwined relationship between myopia and NDDs, suggesting that lifestyle factors may influence both ocular and neurological health through shared biological mechanisms.

The interplay between retinal and brain structural changes, neuroinflammatory responses, neurotransmitter imbalances, genetic predispositions, and environmental exposures may collectively contribute to the observed associations between myopia and NDDs.

Limitations

This study has several limitations. First, although the use of two independent GWAS datasets and comprehensive sensitivity analyses enhanced internal validity, the predominantly European ancestry of the study populations (Finnish and UK Biobank cohorts) may limit the generalizability of our findings. Caution is needed when extrapolating results to populations of diverse ancestries (e.g., Asian cohorts), where genetic architecture, environmental exposures, and disease prevalence may differ, potentially influencing the myopia-NDD relationship. Second, although the bidirectional MR design and rigorous pleiotropy tests (MR-Egger, weighted median, and MR-PRESSO) were employed to minimize confounding, residual horizontal pleiotropy or undetected reverse causality cannot be entirely ruled out. Although sensitivity analyses were conducted to detect and adjust for potential pleiotropy, the inherent limitations of MR methods still warrant cautious interpretation of the causal estimates. Third, the cross-sectional nature of GWAS data restricts the ability to establish temporal causality. Future longitudinal studies that track both myopia progression and NDD onset are needed to validate these findings and further elucidate potential underlying mechanisms.

Conclusion

This bidirectional MR study used two independent GWAS datasets to provide strong evidence against a causal relationship between myopia and four major NDDs. Although no direct causal links were identified, shared biological mechanisms, such

as neuroinflammation and impaired neurotransmitter signaling, may account for the observed co-occurrence of myopia and these conditions. These findings highlight the need for future studies employing advanced neuroimaging techniques and multi-omics approaches to investigate these common molecular and structural pathways, further elucidating the complex interactions between the eye and brain. This study contributes to the growing body of evidence supporting the eye-brain connection and lays the foundation for future investigations into potential shared pathophysiological mechanisms between myopia and NDDs.

Key Points

- Cross-sectional analyses revealed associations between myopia and four neurodegenerative diseases (NDDs).
- Mendelian randomization analyses revealed no bidirectional causal relationship between myopia and the four NDDs.
- Although not directly examined in this study, shared mechanisms, such as structural changes in the retina and brain, neuroinflammation, and genetic predispositions, may underlie the observed associations.
- The eye-brain connection remains a promising area of research for uncovering shared disease pathways and informing early diagnostic and intervention strategies.

Availability of Data and Materials

The datasets used in this study were obtained from the MRC IEU Open GWAS database (http://gwas.mrcieu.ac.uk/) and FinnGen (https://www.finngen.fi/fi), including ALS (ieu-a-1085), MS (ieu-b-18), AD (finn-b-G6_ALZHEIMER), PD (finn-b-G6_PARKINSON), and two myopia-related datasets: myopia (finn-b-H7_MYOPIA) and refractive error (GCST009521). All data in the datasets were derived from individuals of European descent.

Author Contributions

YYF: Investigation, Methodology, Resources, Funding acquisition, Writing—Original Draft; ZJW: Data Curation, Funding acquisition, Software; MAW: Data Curation; LL: Data Curation; LFC: Data Curation, Project Administration, Supervision; BZ: Data Curation, Writing—Review & Editing. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Participants in the included GWAS datasets provided informed consent, and all original studies received approval from relevant institutional ethics review boards.

Since this study utilized publicly available GWAS summary statistics without involving new data collection or direct interaction with human participants, no additional ethical approval was required.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2025.0183.

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