Association of ophthalmic diseases with stroke: cohort study and Mendelian randomization analysis

Chong Li[1,2], Jialiang Chen[3], Ke Li[4,5], Shaojun Zhang[6]*, Siyi Zhu[1,2]*

[1]Rehabilitation Medicine Center and Institute of Rehabilitation Medicine, West China Hospital, Sichuan University, Chengdu, China
[2]Key Laboratory of Rehabilitation Medicine in Sichuan Province, West China Hospital, Sichuan University, Chengdu, China
[3]School of Economics and Management, Shanghai University of Sport, Shanghai, China
[4]Center of Statistical Research, School of Statistics, Southwestern University of Finance and Economics, Chengdu, China
[5]Joint Lab of Data Science and Business Intelligence, School of Statistics, Southwestern University of Finance and Economics, Chengdu, China
[6]Deyang Clinical Research Center for Rehabilitation Medicine, Mianzhu People's Hospital, Mianzhu, Sichuan, China

***Corresponding authors:**
Shaojun Zhang
Deyang Clinical Research Center for Rehabilitation Medicine
Mianzhu People's Hospital
Mianzhu, Sichuan
China
E-mail: zsjlovely@163.com

Siyi Zhu
Rehabilitation Medicine Center and Institute of Rehabilitation Medicine
West China Hospital
Sichuan University
Chengdu, China
E-mail: hxkfzsy@scu.edu.cn

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Stroke ranks as the second leading global cause of death and third major cause of disability, with its incidence and mortality rising sharply between 1990 and 2021, particularly in low- and middle-income countries [1–3]. Identifying modifiable risk factors remains critical for mitigating this burden, as existing preventive measures are not fully effective [4]. Emerging evidence links ophthalmic diseases to stroke risk via vascular or structural ocular alterations [5–7]. However, traditional observational studies are limited by confounders and reverse causality, and most focus on broad stroke categories rather than subtypes [8]. Mendelian randomization (MR) offers a robust approach to address these limitations by using genetic variants to infer causality [9–11]. To address these gaps, the present study aimed to systematically evaluate the bidirectional associations between major stroke subtypes and common ophthalmic diseases by integrating data from the China Health and Retirement Longitudinal Study (CHARLS) with two-sample MR analyses.

Methods. Data were first sourced from the CHARLS [12], a nationally representative survey covering 28 Chinese provinces, targeting adults aged over 45 years. Initiated in 2011 (17,708 baseline participants) with follow-ups in 2013, 2015, and 2018, CHARLS used a computer-assisted personal interviewing system for data collection. Eligible participants (n = 2,759) met the following criteria: complete visual ability and stroke history data, plus continuous follow-up (valid observations: 2,433 in 2013, 2,157 in 2015, 1,413 in 2018). Visual ability (myopia, hyperopia) was assessed via self-reported 5-point scales (reverse-coded; higher scores = poorer function), stroke status via binary self- or informant-reported physician diagnosis. Covariates included sociodemographics (gender, age, residence) and health behaviors (alcohol, smoking, activity). For two-sample bidirectional MR, data were restricted to European descent to minimize population stratification. Stroke subtype genetic data (AIS: 17,265 cases; CES: 7,193 cases; LAS: 4,373 cases; SVS: 5,386 cases) came from the MEGASTROKE consortium (34,217 cases and 406,111 controls);

ophthalmic trait data (myopia, glaucoma, etc.) from UK Biobank and FinnGen. Missing single-nucleotide polymorphism (SNP) data were imputed per original GWAS methods; rare variants (MAF < 1%) were excluded. SNPs (instrumental variables) met genome-wide significance ($p \leq 5 \times 10^{-6}$, adjusted to 5×10^{-5} if limited) and no high linkage disequilibrium ($r^2 \geq 0.001$, distance > 10,000 kb). MR adhered to three assumptions: SNP-exposure association, no SNP-confounder correlation, and exposure-mediated outcome effect. Eight ophthalmic traits and four stroke subtypes were analyzed.

Statistical analysis. For CHARLS-based analysis, time-varying Cox regression estimated HR (95% CI) for visual ability-stroke association (follow-up as time scale). Sensitivity analyses excluded sociodemographic/health behavior covariates to test robustness. Analyses were conducted using STATA 17; two-tailed $p < 0.05$ was significant. For MR-based analysis, the primary approach was inverse-variance weighted (IVW); supplementary methods included weighted median and MR-Egger. Sensitivity analyses (funnel plots, leave-one-out, Cochran's Q, MR-Egger intercept) were performed to assess bias and pleiotropy. Analyses were conducted using the R packages Two-Sample MR (v0.4.25) and MRPRESSO (v1.0); a SNP threshold of $p \leq 5 \times 10^{-6}$ was applied to minimize false positives.

Results. A total of 6,787 participants from the 2011 CHARLS baseline were included in the final analysis, with a mean age of 63.86 years (SD = 11.00); 45.85% were male (1,494 participants) and 54.15% were female (1,265 participants). Time-varying Cox regression models were used to analyze the relationship between visual ability and stroke risk, and the results showed a significant positive association between both myopia and hyperopia and stroke risk. Specifically, each one-point increase in myopia severity was associated with a 41.9% higher risk of stroke (HR = 1.419, 95% CI: 1.199–1.680), while each one-point increase in hyperopia severity was linked to a 26.0% increased stroke risk (HR = 1.260, 95% CI: 1.067–1.487). Sensitivity analyses were conducted by excluding different categories of covariates. When sociodemographic variables were excluded, myopia (HR = 1.360, 95% CI: 1.184–1.564) and hyperopia (HR = 1.312, 95% CI: 1.140–1.510) remained significantly associated with elevated stroke risk. When health behavior variables were excluded, the associations persisted, with myopia increasing stroke risk by 29.2% (HR = 1.292, 95% CI: 1.145–1.457) and hyperopia by 21.7% (HR = 1.217, 95% CI: 1.080–1.371). These sensitivity analyses confirmed that declining visual function – whether myopia or hyperopia – was strongly and positively associated with higher stroke risk.

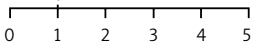
For arterial ischemic stroke (AIS), IVW analysis showed that right-eye myopia (OR = 2.28, 95% CI: 1.256–3.950, $p = 0.006$) and genetically predicted peripheral retinal degeneration (PRD; OR = 1.014, 95% CI: 1.005–1.023, $p = 0.003$) were causally associated with increased AIS risk, with consistent results from MR-Egger and weighted median methods. No causal relationships were found between AIS and left-eye myopia, glaucoma, cataracts, presbyopia, or age-related macular degeneration (AMD). For cardioembolic stroke (CES), IVW analysis revealed that right-eye myopia (OR = 5.102, 95% CI: 1.613–16.142, $p = 0.006$) and PRD (OR = 1.022, 95% CI: 1.004–1.041, $p = 0.017$) were causally linked to higher CES risk, while other ophthalmic traits showed no significant associations. For large artery stroke (LAS), IVW analysis indicated causal associations between left-eye myopia (OR = 7.772, 95% CI: 1.160–52.066, $p = 0.035$), right-eye myopia (OR = 9.605, 95% CI: 2.281–40.453, $p = 0.002$) and increased LAS risk, with other MR methods yielding consistent significant results. For small vessel stroke (SVS), IVW analysis found that right-eye myopia (OR = 5.993, 95% CI: 1.466–24.505, $p = 0.013$) and PRD (OR = 1.022, 95% CI: 1.002–1.043, $p = 0.029$) were causally associated with higher SVS risk. In addition, MR-Egger also confirmed a significant association for right-eye myopia (OR = 118.736, 95% CI: 6.924–2036.160, $p = 0.005$) (Figure 1). Sensitivity analyses (MR-Egger intercept test, Cochran's Q statistic, leave-one-out analysis) for all stroke subtypes showed no horizontal pleiotropy or significant heterogeneity in SNP effects, and symmetric funnel plots indicated no estimation bias, confirming the robustness of the findings (Table I).

Reverse MR analysis showed that genetically increased AIS risk was causally associated with a higher likelihood of diabetic retinopathy (DR; IVW: OR = 1.136, 95% CI: 1.053–1.227, $p = 0.001$), with the weighted median method also supporting this association (OR = 1.122, 95% CI: 1.011–1.245, $p = 0.030$), though MR-Egger and weighted mode results were not significant. Sensitivity analyses for this association revealed no horizontal pleiotropy (MR-Egger intercept = 0.001, $p = 0.873$) or significant heterogeneity (Cochran's Q = 48.928, $p = 0.157$), and leave-one-out analysis confirmed that no single SNP disproportionately influenced the causal estimate. No substantial causal relationships were identified between other stroke subtypes (CES, LAS, SVS) and any ophthalmic disease phenotypes (myopia, glaucoma, cataracts, presbyopia, PRD, AMD) (Table II).

Discussion. This study integrated the CHARLS epidemiological survey and bidirectional two-sample MR analysis to explore the association between visual ability and stroke risk. CHARLS re-

A

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
Left eye myopia	13	IVW	0.579 (0.273 to 1.227)	0.154
		MR Egger	0.412 (0.055 to 3.097)	0.409
		Weighted median	0.434 (0.162 to 1.163)	0.097
		Weighted node	0.336 (0.075 to 1.499)	0.181
Right eye myopia	23	IVW	2.228 (1.256 to 3.950)	0.006
		MR Egger	5.533 (1.695 to 18.064)	0.013
		Weighted median	2.867 (1.312 to 6.268)	0.008
		Weighted node	3.779 (0.920 to 15.527)	0.084
Glaucoma	47	IVW	12.218 (0.721 to 206.959)	0.083
		MR Egger	0.045 (0.000 to 342.322)	0.500
		Weighted median	1.909 (0.044 to 82.717)	0.737
		Weighted node	0.951 (0.002 to 482.338)	0.987
Cataract	29	IVW	15.376 (0.002 to 106369.608)	0.545
		MR Egger	0.000 (0.000 to 10539.761)	0.089
		Weighted median	710.858 (0.029 to 17359872.670)	0.203
		Weighted node	73602.152 (0.000 to 24507900000000.000)	0.274
Diabetic retinopathy	17	IVW	1.045 (0.968 to 1.128)	0.257
		MR Egger	1.341 (1.063 to 1.691)	0.027
		Weighted median	1.042 (0.947 to 1.147)	0.399
		Weighted node	0.986 (0.850 to 1.144)	0.855
Presbyopia	47	IVW	0.786 (0.226 to 2.729)	0.704
		MR Egger	0.643 (0.037 to 11.255)	0.764
		Weighted median	0.692 (0.149 to 3.213)	0.638
		Weighted node	0.598 (0.035 to 10.198)	0.724
Peripheral retinal degeneration	9	IVW	1.014 (1.005 to 1.023)	0.003
		MR Egger	1.013 (1.003 to 1.024)	0.049
		Weighted median	1.013 (1.001 to 1.026)	0.035
		Weighted node	1.013 (1.002 to 1.024)	0.056
Age-related macular degeneration	31	IVW	1.005 (0.981 to 1.029)	0.686
		MR Egger	1.015 (0.973 to 1.060)	0.493
		Weighted median	0.997 (0.965 to 1.029)	0.831
		Weighted node	0.998 (0.966 to 1.032)	0.920



B

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
Left eye myopia	13	IVW	0.493 (0.109 to 2.221)	0.357
		MR Egger	5.807 (0.101 to 333.558)	0.415
		Weighted median	0.427 (0.063 to 2.898)	0.384
		Weighted node	0.393 (0.024 to 6.493)	0.527
Right eye myopia	23	IVW	5.102 (1.613 to 16.142)	0.006
		MR Egger	5.293 (0.469 to 59.748)	0.199
		Weighted median	7.371 (1.580 to 34.387)	0.011
		Weighted node	8.464 (0.523 to 137.079)	0.154
Glaucoma	47	IVW	1.994 (0.011 to 371.113)	0.796
		MR Egger	0.000 (0.000 to 0.832)	0.054
		Weighted median	0.048 (0.000 to 60.661)	0.404
		Weighted node	0.044 (0.000 to 392.348)	0.505
Cataract	29	IVW	18.318 (0.000 to 39995428.760)	0.696
		MR Egger	0.000 (0.000 to 3191200000000.000)	0.121
		Weighted median	0.415 (0.000 to 65829354.750)	0.927
		Weighted node	0.291 (0.000 to 757484000000000.000)	0.946
Diabetic retinopathy	17	IVW	1.020 (0.890 to 1.169)	0.774
		MR Egger	1.010 (0.679 to 1.502)	0.962
		Weighted median	1.030 (0.867 to 1.225)	0.735
		Weighted node	0.990 (0.775 to 1.266)	0.939
Presbyopia	47	IVW	0.332 (0.039 to 2.856)	0.315
		MR Egger	0.306 (0.002 to 47.961)	0.649
		Weighted median	0.136 (0.007 to 2.663)	0.189
		Weighted node	0.038 (0.000 to 7.007)	0.225
Peripheral retinal degeneration	9	IVW	1.022 (1.004 to 1.041)	0.017
		MR Egger	1.021 (0.999 to 1.042)	0.108
		Weighted median	1.023 (0.999 to 1.046)	0.058
		Weighted node	1.018 (0.996 to 1.041)	0.150
Age-related macular degeneration	31	IVW	0.990 (0.947 to 1.036)	0.675
		MR Egger	0.999 (0.931 to 1.072)	0.972
		Weighted median	0.968 (0.924 to 1.015)	0.180
		Weighted node	0.971 (0.930 to 1.014)	0.196

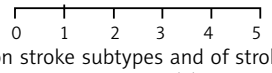
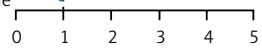


Figure 1. Causal effects of ophthalmic diseases on stroke subtypes and of stroke on ophthalmic diseases (**A**–**D**). Causal effects of ophthalmic diseases on different stroke subtypes: (**A**) arterial ischemic stroke (AIS), (**B**) cardioembolic stroke (CES)

C

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
Left eye myopia	13	IVW	7.772 (1.160 to 52.066)	0.035
		MR Egger	83.672 (0.507 to 13809.830)	0.120
		Weighted median	1.694 (0.123 to 23.287)	0.693
		Weighted node	1.118 (0.019 to 66.606)	0.958
Right eye myopia	23	IVW	9.605 (2.281 to 40.453)	0.002
		MR Egger	107.632 (5.616 to 2062.676)	0.007
		Weighted median	15.613 (1.879 to 129.717)	0.011
		Weighted node	42.137 (1.333 to 1332.295)	0.050
Glaucoma	47	IVW	9.078 (0.009 to 9383.409)	0.533
		MR Egger	2.132 (0.000 to 9184983839.000)	0.947
		Weighted median	184.076 (0.008 to 4415050.344)	0.311
		Weighted node	118.099 (0.000 to 309378033.500)	0.530
Cataract	29	IVW	4787.119 (0.000 to 445972000000.00)	0.365
		MR Egger	0.000 (0.000 to 0.000)	0.026
		Weighted median	1248.113 (0.000 to 22788400000000.000)	0.554
		Weighted node	0.066 (0.000 to 20213300000000000000.000)	0.911
Diabetic retinopathy	17	IVW	0.909 (0.744 to 1.111)	0.351
		MR Egger	1.113 (0.640 to 1.935)	0.710
		Weighted median	0.808 (0.640 to 1.020)	0.073
		Weighted node	0.717 (0.509 to 1.009)	0.076
Presbyopia	47	IVW	7.324 (0.510 to 105.152)	0.143
		MR Egger	4.912 (0.010 to 2434.198)	0.618
		Weighted median	18.726 (0.504 to 695.775)	0.112
		Weighted node	158.794 (0.083 to 304164.361)	0.195
Peripheral retinal degeneration	9	IVW	1.021 (1.000 to 1.043)	0.054
		MR Egger	1.017 (0.993 to 1.042)	0.213
		Weighted median	1.028 (0.997 to 1.060)	0.074
		Weighted node	1.026 (0.998 to 1.056)	0.111
Age-related macular degeneration	31	IVW	0.984 (0.938 to 1.033)	0.514
		MR Egger	0.932 (0.869 to 1.000)	0.061
		Weighted median	0.952 (0.897 to 1.010)	0.102
		Weighted node	0.954 (0.904 to 1.006)	0.095



D

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
Left eye myopia	13	IVW	1.315 (0.222 to 7.808)	0.763
		MR Egger	0.195 (0.002 to 22.866)	0.516
		Weighted median	1.444 (0.119 to 17.525)	0.773
		Weighted node	1.446 (0.028 to 73.675)	0.857
Right eye myopia	23	IVW	5.993 (1.466 to 24.505)	0.013
		MR Egger	118.736 (6.924 to 2036.160)	0.005
		Weighted median	3.082 (0.447 to 21.242)	0.253
		Weighted node	1.873 (0.054 to 64.825)	0.733
Glaucoma	47	IVW	0.805 (0.003 to 228.492)	0.940
		MR Egger	0.001 (0.000 to 97411.254)	0.473
		Weighted median	0.007 (0.000 to 36.639)	0.256
		Weighted node	0.001 (0.000 to 3136.873)	0.368
Cataract	29	IVW	0.089 (0.000 to 574595.190)	0.762
		MR Egger	0.000 (0.000 to 84300000000000000000.000)	0.480
		Weighted median	0.974 (0.000 to 808792672.800)	0.998
		Weighted node	0.068 (0.000 to 601515000000000000.000)	0.985
Diabetic retinopathy	17	IVW	0.974 (0.803 to 1.182)	0.790
		MR Egger	0.702 (0.412 to 1.195)	0.212
		Weighted median	1.084 (0.869 to 1.352)	0.474
		Weighted node	1.271 (0.807 to 2.002)	0.316
Presbyopia	47	IVW	3.922 (0.298 to 51.669)	0.299
		MR Egger	16883.936 (62.572 to 4555793.477)	0.001
		Weighted median	4.690 (0.118 to 187.116)	0.411
		Weighted node	8.150 (0.002 to 41262.802)	0.632
Peripheral retinal degeneration	9	IVW	1.022 (1.002 to 1.043)	0.029
		MR Egger	1.025 (1.001 to 1.019)	0.080
		Weighted median	1.019 (0.993 to 1.046)	0.151
		Weighted node	1.018 (0.993 to 1.043)	0.206
Age-related macular degeneration	31	IVW	0.989 (0.937 to 1.043)	0.675
		MR Egger	1.066 (0.970 to 1.172)	0.196
		Weighted median	1.015 (0.948 to 1.087)	0.660
		Weighted node	1.024 (0.95 to 1.100)	0.522

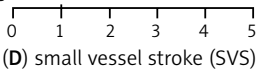
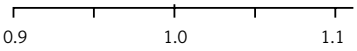


Figure 1. Cont. (**C**) large artery stroke (LAS), and (**D**) small vessel stroke (SVS)

E

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
AIS	48	IVW	1.004 (0.994 to 1.013)	0.471
		MR Egger	0.989 (0.960 to 1.018)	0.449
		Weighted median	1.003 (0.988 to 1.018)	0.704
		Weighted node	1.000 (0.972 to 1.029)	0.997
LAS	39	IVW	1.003 (0.999 to 1.008)	0.135
		MR Egger	1.003 (0.993 to 1.012)	0.591
		Weighted median	1.006 (0.999 to 1.012)	0.084
		Weighted node	1.007 (0.995 to 1.020)	0.272
CES	37	IVW	1.001 (0.995 to 1.006)	0.811
		MR Egger	0.994 (0.982 to 1.005)	0.291
		Weighted median	1.003 (0.994 to 1.012)	0.508
		Weighted node	1.004 (0.990 to 1.018)	0.586
SVS	34	IVW	0.999 (0.993 to 1.005)	0.668
		MR Egger	0.983 (0.973 to 0.994)	0.004
		Weighted median	1.000 (0.992 to 1.009)	0.904
		Weighted node	1.007 (0.989 to 1.025)	0.438



F

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
AIS	48	IVW	0.998 (0.987 to 1.009)	0.718
		MR Egger	1.023 (0.991 to 1.055)	0.176
		Weighted median	0.995 (0.981 to 1.010)	0.504
		Weighted node	1.017 (0.981 to 1.055)	0.353
LAS	39	IVW	0.999 (0.994 to 1.003)	0.585
		MR Egger	0.994 (0.985 to 1.003)	0.187
		Weighted median	0.997 (0.991 to 1.003)	0.366
		Weighted node	0.997 (0.984 to 1.011)	0.681
CES	37	IVW	0.998 (0.992 to 1.003)	0.422
		MR Egger	1.008 (0.996 to 1.020)	0.189
		Weighted median	0.998 (0.989 to 1.007)	0.665
		Weighted node	1.008 (0.994 to 1.022)	0.290
SVS	34	IVW	0.997 (0.992 to 1.002)	0.240
		MR Egger	0.998 (0.987 to 1.009)	0.733
		Weighted median	0.997 (0.990 to 1.004)	0.425
		Weighted node	1.000 (0.986 to 1.013)	0.970

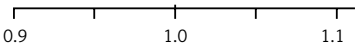
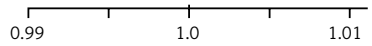


Figure 1. Cont. **E–L** – Causal effects of stroke (AIS, CES, LAS, SVS) on different ophthalmic diseases: (**E**) left-eye myopia, (**F**) right-eye myopia

G

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
AIS	48	IVW	1.000 (0.998 to 1.001)	0.609
		MR Egger	0.999 (0.993 to 1.005)	0.717
		Weighted median	1.000 (0.998 to 1.003)	0.667
		Weighted node	1.001 (0.997 to 1.006)	0.535
LAS	39	IVW	1.000 (0.999 to 1.001)	0.683
		MR Egger	0.998 (0.994 to 1.003)	0.419
		Weighted median	1.000 (0.999 to 1.002)	0.802
		Weighted node	1.001 (0.998 to 1.003)	0.609
CES	37	IVW	1.000 (0.999 to 1.001)	0.625
		MR Egger	1.000 (0.998 to 1.003)	0.822
		Weighted median	1.000 (0.999 to 1.002)	0.512
		Weighted node	1.000 (0.999 to 1.002)	0.552
SVS	34	IVW	1.000 (0.999 to 1.001)	0.846
		MR Egger	1.000 (0.995 to 1.005)	0.973
		Weighted median	1.000 (0.999 to 1.002)	0.479
		Weighted node	1.001 (0.998 to 1.003)	0.585



H

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
AIS	48	IVW	1.000 (0.998 to 1.001)	0.936
		MR Egger	1.000 (0.992 to 1.008)	0.925
		Weighted median	0.999 (0.998 to 1.001)	0.392
		Weighted node	0.999 (0.996 to 1.001)	0.351
LAS	39	IVW	1.000 (0.999 to 1.001)	0.888
		MR Egger	0.992 (0.986 to 0.998)	0.087
		Weighted median	1.000 (0.999 to 1.002)	0.499
		Weighted node	1.001 (0.999 to 1.004)	0.380
CES	37	IVW	1.000 (0.999 to 1.000)	0.328
		MR Egger	1.000 (0.998 to 1.001)	0.718
		Weighted median	1.000 (0.999 to 1.000)	0.402
		Weighted node	1.000 (0.999 to 1.001)	0.414
SVS	34	IVW	1.000 (0.999 to 1.001)	0.593
		MR Egger	0.995 (0.987 to 1.003)	0.294
		Weighted median	1.000 (0.999 to 1.001)	0.754
		Weighted node	1.000 (0.998 to 1.001)	0.709

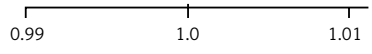
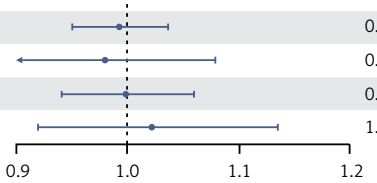


Figure 1. Cont. **E–L** – Causal effects of stroke (AIS, CES, LAS, SVS) on different ophthalmic diseases: (**G**) glaucoma, (**H**) cataract

I

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
AIS	48	IVW	1.136 (1.053 to 1.227)	0.001
		MR Egger	1.117 (0.895 to 1.395)	0.334
		Weighted median	1.122 (1.011 to 1.245)	0.030
		Weighted node	1.127 (0.914 to 1.390)	0.269
LAS	39	IVW	1.011 (0.983 to 1.040)	0.434
		MR Egger	0.979 (0.930 to 1.030)	0.411
		Weighted median	1.012 (0.970 to 1.055)	0.577
		Weighted node	0.999 (0.939 to 1.061)	0.963
CES	37	IVW	1.027 (0.986 to 1.070)	0.199
		MR Egger	1.006 (0.917 to 1.104)	0.894
		Weighted median	1.063 (1.000 to 1.129)	0.050
		Weighted node	1.063 (0.988 to 1.145)	0.112
SVS	34	IVW	0.993 (0.951 to 1.037)	0.741
		MR Egger	0.980 (0.891 to 1.078)	0.686
		Weighted median	0.999 (0.941 to 1.060)	0.966
		Weighted node	1.022 (0.920 to 1.135)	0.690



J

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
AIS	48	IVW	1.001 (0.997 to 1.005)	0.571
		MR Egger	1.000 (0.989 to 1.011)	0.988
		Weighted median	1.003 (0.998 to 1.008)	0.265
		Weighted node	1.008 (0.996 to 1.019)	0.194
LAS	39	IVW	0.999 (0.997 to 1.000)	0.089
		MR Egger	0.999 (0.996 to 1.002)	0.615
		Weighted median	0.999 (0.997 to 1.001)	0.331
		Weighted node	0.998 (0.993 to 1.002)	0.377
CES	37	IVW	1.000 (0.998 to 1.002)	0.784
		MR Egger	0.999 (0.995 to 1.003)	0.677
		Weighted median	1.001 (0.998 to 1.004)	0.659
		Weighted node	1.002 (0.997 to 1.006)	0.416
SVS	34	IVW	1.000 (0.998 to 1.002)	0.702
		MR Egger	0.997 (0.993 to 1.001)	0.117
		Weighted median	0.999 (0.997 to 1.002)	0.452
		Weighted node	0.999 (0.994 to 1.003)	0.584

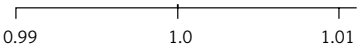
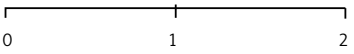


Figure 1. Cont. **E–L** – Causal effects of stroke (AIS, CES, LAS, SVS) on different ophthalmic diseases: (**I**) diabetic retinopathy, (**J**) presbyopia

K

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
AIS	48	IVW	0.972 (0.608 to 1.554)	0.907
		MR Egger	1.047 (0.269 to 4.079)	0.948
		Weighted median	1.176 (0.669 to 2.067)	0.573
		Weighted node	1.598 (0.511 to 4.994)	0.425
LAS	39	IVW	1.102 (0.947 to 1.283)	0.207
		MR Egger	1.076 (0.818 to 1.415)	0.604
		Weighted median	1.103 (0.873 to 1.393)	0.413
		Weighted node	1.078 (0.793 to 1.465)	0.637
CES	37	IVW	0.919 (0.728 to 1.159)	0.475
		MR Egger	1.266 (0.757 to 2.119)	0.375
		Weighted median	0.827 (0.588 to 1.164)	0.276
		Weighted node	0.795 (0.509 to 1.242)	0.320
SVS	34	IVW	0.870 (0.688 to 1.102)	0.248
		MR Egger	0.873 (0.518 to 1.470)	0.613
		Weighted median	0.806 (0.578 to 1.125)	0.206
		Weighted node	0.766 (0.434 to 1.352)	0.366



L

Exposure	No. of SNP	Method	OR (95% CI)	*P*-value
AIS	48	IVW	1.031 (0.874 to 1.217)	0.716
		MR Egger	0.898 (0.557 to 1.448)	0.661
		Weighted median	1.033 (0.839 to 1.273)	0.759
		Weighted node	1.314 (0.796 to 2.169)	0.293
LAS	39	IVW	0.972 (0.910 to 1.038)	0.395
		MR Egger	1.009 (0.895 to 1.137)	0.890
		Weighted median	0.950 (0.870 to 1.037)	0.249
		Weighted node	0.898 (0.754 to 1.069)	0.236
CES	37	IVW	1.022 (0.946 to 1.105)	0.581
		MR Egger	0.982 (0.825 to 1.168)	0.836
		Weighted median	1.095 (0.978 to 1.226)	0.117
		Weighted node	1.127 (0.963 to 1.318)	0.146
SVS	34	IVW	0.933 (0.856 to 1.017)	0.117
		MR Egger	0.882 (0.727 to 1.070)	0.215
		Weighted median	0.942 (0.838 to 1.060)	0.323
		Weighted node	0.903 (0.739 to 1.104)	0.329

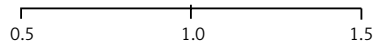


Figure 1. Cont. **E–L** – Causal effects of stroke (AIS, CES, LAS, SVS) on different ophthalmic diseases: (**K**) peripheral retinal degeneration, and (**L**) age-related macular degeneration

vealed that myopia and hyperopia were positively associated with stroke incidence in Chinese adults aged over 45 years, highlighting the value of visual assessment in public health screening. MR analysis provided genetic-level causal evidence, linking peripheral retinal degeneration and myopia to increased risks of acute ischemic stroke and other subtypes. The two approaches complemented each other: CHARLS reflected real-world associations, while MR reduced confounding bias. Potential mechanisms involve vascular and inflammatory pathways [13–15]. Clinically, visual ability evaluation should be incorporated into stroke risk assessment, especially in aging populations with high myopia prevalence. Limitations include self-report bias in CHARLS and the European-centric genetic data in MR, calling for future studies in diverse cohorts with objective ophthalmic measures.

In conclusion, this study combined CHARLS data and bidirectional MR analysis to explore visual ability-stroke associations. Results from

Table I. Sensitivity analysis examining the causal association between stroke and ophthalmic diseases

Exposure	Outcome	Cochran Q test		MR-Egger	
		Q value	*P*-value	Intercept	*P*-value
Left eye myopia	AIS	5.572	0.900	0.007	0.730
Right eye myopia		11.648	0.768	–0.021	0.106
Glaucoma		56.314	0.069	0.008	0.203
Cataract		42.772	0.015	0.058	0.079
Diabetic retinopathy		17.802	0.273	–0.023	0.044
Presbyopia		64.351	0.038	0.001	0.879
Peripheral retinal degeneration		3.306	0.855	0.002	0.803
Age-related macular degeneration		27.013	0.409	–0.003	0.573
Left eye myopia	CES	8.939	0.628	–0.052	0.228
Right eye myopia		12.146	0.668	–0.001	0.974
Glaucoma		52.046	0.138	0.025	0.035
Cataract		31.426	0.175	0.087	0.112
Diabetic retinopathy		21.580	0.157	0.001	0.959
Presbyopia		50.363	0.305	0.000	0.973
Peripheral retinal degeneration		3.919	0.789	0.004	0.744
Age-related macular degeneration		45.087	0.016	–0.003	0.764
Left eye myopia	LAS	8.214	0.694	–0.051	0.349
Right eye myopia		14.740	0.544	–0.055	0.086
Glaucoma		51.147	0.133	0.002	0.893
Cataract		29.524	0.243	0.157	0.021
Diabetic retinopathy		24.403	0.059	–0.021	0.453
Presbyopia		26.728	0.990	0.002	0.890
Peripheral retinal degeneration		7.544	0.479	0.010	0.534
Age-related macular degeneration		31.098	0.267	0.021	0.057
Left eye myopia	SVS	9.036	0.619	0.041	0.417
Right eye myopia		15.970	0.384	–0.066	0.054
Glaucoma		39.115	0.598	0.010	0.465
Cataract		22.259	0.621	0.041	0.495
Diabetic retinopathy		29.216	0.023	0.034	0.216
Presbyopia		51.099	0.280	–0.041	0.002
Peripheral retinal degeneration		8.395	0.396	–0.007	0.650
Age-related macular degeneration		23.523	0.603	–0.022	0.068

CHARLS indicated that both myopia and hyperopia were positively correlated with an increased risk of stroke among Chinese adults. Complementarily, MR analysis revealed genetic evidence linking PRD and myopia to specific stroke subtypes, while also identifying a reverse causal relationship between AIS and DR. Together, these findings suggest that assessing visual function may aid in stroke risk stratification, particularly in regions with high myopia prevalence, and highlight the importance of enhanced DR screening among AIS patients with diabetes. Nonetheless, potential recall bias in the CHARLS data and the limited generalizability of the MR findings should be acknowledged. Future studies should incorporate more diverse populations and objective measurements to further elucidate underlying causal pathways.

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Table II. Sensitivity analysis examining the causal association between stroke and ophthalmic diseases

Exposure	Outcome	Cochran Q test		MR-Egger	
		Q value	*P*-value	Intercept	*P*-value
AIS	Left eye myopia	43.494	0.619	0.001	0.292
	Right eye myopia	55.144	0.194	–0.002	0.119
	Glaucoma	30.374	0.346	0.000	0.800
	Cataract	37.575	0.010	0.000	0.935
	Diabetic retinopathy	48.928	0.157	0.001	0.873
	Presbyopia	58.325	0.059	0.000	0.824
	Peripheral retinal degeneration	61.688	0.015	–0.006	0.910
	Age-related macular degeneration	60.139	0.021	0.011	0.548
CES	Left eye myopia	33.570	0.489	0.001	0.181
	Right eye myopia	29.861	0.671	–0.002	0.055
	Glaucoma	21.093	0.392	0.000	0.945
	Cataract	10.947	0.690	0.000	0.985
	Diabetic retinopathy	35.774	0.385	0.003	0.633
	Presbyopia	38.509	0.234	0.000	0.744
	Peripheral retinal degeneration	38.899	0.259	–0.054	0.182
	Age-related macular degeneration	31.421	0.595	0.007	0.615
LAS	Left eye myopia	24.576	0.882	0.000	0.818
	Right eye myopia	32.433	0.593	0.002	0.224
	Glaucoma	10.821	0.372	0.000	0.363
	Cataract	8.161	0.086	0.001	0.082
	Diabetic retinopathy	32.968	0.518	0.012	0.140
	Presbyopia	30.494	0.543	0.000	0.697
	Peripheral retinal degeneration	31.186	0.606	0.009	0.836
	Age-related macular degeneration	49.549	0.041	–0.013	0.474
SVS	Left eye myopia	42.483	0.102	0.004	0.002
	Right eye myopia	27.840	0.677	0.000	0.797
	Glaucoma	14.438	0.344	0.000	0.995
	Cataract	9.123	0.332	0.001	0.271
	Diabetic retinopathy	19.379	0.886	0.003	0.774
	Presbyopia	39.624	0.112	0.001	0.112
	Peripheral retinal degeneration	24.237	0.669	–0.001	0.990
	Age-related macular degeneration	29.886	0.369	0.012	0.531

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Ethical approval

The original CHARLS project was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015).

Conflict of interest

The authors declare no conflict of interest.

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