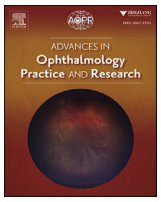
Advances in Ophthalmology Practice and Research 4 (2024) 147–155

Contents lists available at ScienceDirect

Advances in Ophthalmology Practice and Research

journal homepage: www.journals.elsevier.com/advances-in-ophthalmology-practice-and-research



Full Length Article

Association between glaucoma and stroke: A bidirectional mendelian randomization study

Kai Wang [a,1], Xueqi Lin [b,c,1], Siting Sheng [a], Dan Chen [a], Xin Liu [a], Ke Yao [a,*]

[a] Eye Center of the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
[b] Department of Ophthalmology, Zhongshan Hospital, Fudan University, Shanghai, China
[c] Shanghai Institute of Infectious Disease and Biosecurity, Zhongshan Hospital, Fudan University, Shanghai, China

ARTICLE INFO

Keywords:
Glaucoma
Stroke
Mendelian randomization
Causation
Metabolic-related trait

ABSTRACT

Purpose: Observational studies have reported positive associations between glaucoma and stroke; however, controversial results exist. Importantly, the nature of the relationship remains unknown since previous studies were not designed to test causality. Therefore, we aimed to investigate the possible causal relationships between glaucoma and stroke.

Methods: Our two-sample Mendelian randomization (MR) encompassed multi-ethnic large-scale genome-wide association studies with more than 20000 cases and 260000 controls for glaucoma, and more than 80000 cases and 630000 controls for stroke. Individual effect estimates for each SNP were combined using the inverse-variance weighted (IVW) method. To avoid potential pleiotropic effects, we adjusted the main results by excluding genetic variants associated with metabolic factors. The weighted median and MR-Egger methods were also used for the sensitivity analysis.

Results: Our MR analysis revealed that glaucoma and its subtypes, including primary open-angle glaucoma and primary angle-closure glaucoma, exhibited no causal role in relation to any stroke (AS), any ischemic stroke (AIS), large-artery atherosclerotic stroke (LAS), small-vessel stroke (SVS), or cardioembolic stroke (CES) across MR analyses (all $P > 0.05$). The null associations remained robust even after adjusting for metabolic-related traits and were consistent in both the European and Asian populations. Furthermore, reverse MR analyses also did not indicate any significant causal effects of AS, AIS, LAS, or CES on glaucoma risk.

Conclusions: Evidence from our series of causal inference approaches using large-scale population-based MR analyses did not support causal effects between glaucoma and stroke. These findings suggest that the relationship of glaucoma management and stroke risk prevention should be carefully evaluated in future studies. In turn, stroke diagnosis should not be simply applied to glaucoma risk prediction.

1. Introduction

Stroke is a leading cause of disability and a major cause of mortality worldwide.[1] Secondary stroke prevention lies in deciphering the most likely stroke mechanism. In general, controlling vascular risk factors is one of the main goals in stroke prevention.[2] Ocular conditions have been suggested as a significant comorbidity in vascular disability related to stroke, with approximately 60% of people with chronic stroke reporting ocular deficits.[1,3–5] Among stroke survivors, comorbid glaucoma is particularly common, especially among older adults.[6,7]

Glaucoma is a well-known multifactorial disease that leads to the acquired loss of retinal ganglion cells and axons within the optic nerve, causing optic neuropathy and a corresponding progressive loss of visual fields.[8] Due to its often-asymptomatic nature until a relatively late stage, diagnosis is frequently delayed.[9]

The pathogenesis of glaucoma is proposed to involve two major theories: "the mechanical theory" and "the vascular theory". Elevated intraocular pressure is a well-known major risk factor for glaucoma. In addition, growing evidences suggest that vascular factors may play a crucial role in glaucoma pathogenesis.[10,11] Stroke acting as a representative vascular disease,[12] highlighting the clinical and biological relevance of investigating the relationship between glaucoma and stroke.

* Corresponding author.Eye Center of the 2nd Affiliated Hospital, Zhejiang University School of Medicine, 88 Jiefang Road, Hangzhou 310009, Zhejiang Province, China.
E-mail address: xlren@zju.edu.cn (K. Yao).
[1] These authors have contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.aopr.2024.04.003
Received 6 December 2023; Received in revised form 25 March 2024; Accepted 15 April 2024
Available online 23 April 2024

Previous observational studies have substantially reported positive associations between glaucoma subtypes and the risk of stroke,[13–19] especially among Asian populations.[13–18] However, the causal nature of this relationship remains unknown, as circulation disabilities are assumed to be common factors in the occurrence or progression of both stroke and glaucoma.[20,21] Reverse causality also makes sense, as cerebrovascular disease may be a potential risk factor for glaucomatous optic nerve damage.[22–25] More importantly, conflicting evidences exists regarding this relationship, and after adjusting for selected risk factors, the association between stroke risk and glaucoma shows no overall statistical significance.[26] In a study involving patients with diabetes, glaucoma was not associated with an increased risk of stroke mortality.[27] Since observational studies are characterized by potential confounding factors, the biological basis for the associations between glaucoma and stroke risk has not yet been firmly established.

Mendelian randomization (MR) is often used to evaluate the causality of risk factors for outcomes of interest. Causality can be inferred because the alleles of a particular exposure-associated genotype are randomly assigned at conception. This random assignment helps minimize the bias introduced by confounding factors and reverse causation in conventional observational studies.[28] Previous MR studies have investigated the effect of circulating metabolites on the risk of glaucoma,[29] the causal relationship between risk of T2D and glaucoma,[30] and various risk factors for stroke progression.[31–34] However, to the best of our knowledge, no MR study has investigated the causal relationship between glaucoma and stroke risk. Therefore, we have incorporated the largest available datasets to examine the potential effect of glaucoma and its subtypes on stroke risk, encompassing any stroke (AS), any ischemic stroke (AIS), large-artery atherosclerotic stroke (LAS), small-vessel stroke (SVS), and cardioembolic stroke (CES). Further, stratified analyses have been conducted for glaucoma subtypes and different populations. On the other hand, we have also investigated whether a predisposition to the aforementioned stroke subtypes affects the occurrence or progression of glaucoma.

2. Material and methods

2.1. Study design

We explored the relationship between glaucoma and stroke by conducting a two-sample MR study using summary statistics from two different studies, in order to determine the causal effect of glaucoma and its subtypes on stroke. Additionally, we employed MR to investigate whether a predisposition to stroke is likely to impact glaucoma risk.

The studies included in our research have received ethical approval from relevant institutional review boards. According to the institutional review board of the Second Affiliated Hospital of Zhejiang University School of Medicine, as we utilized publicly available summary-level data from the published genome-wide meta-analysis, no additional ethical approval was required.

2.2. Data sources

Summary statistics for the association between single-nucleotide polymorphisms (SNPs) and glaucoma were extracted from a meta-analysis that combined the Genetic Epidemiology Research in Adult Health and Aging (GERA) cohort and the UK Biobank (UKBB), involving 240302 individuals, including 214102 European, 5189 Hispanic or Latin American, 6950 African, 10490 Asian, and 3571 participants of other mixed ancestry.[35] Specifically, genetic associations with primary open-angle glaucoma (POAG) were obtained from GERA, including 51901 European, 5189 Hispanic or Latin American, 1847 African, and 4475 Asian.[35] Genetic associations with primary angle-closure glaucoma (PACG) were obtained from case-control collections enrolled from 15 countries, including 5516 Europeans and 20938 Asians.[36] Genetic associations with POAG were obtained from a meta-analysis of Biobank Japan (BBJ), the Japan Multi-Institutional Collaborative Cohort Study (J-MICC), and the Japan Public Health Center-based Prospective Study (JPHC), involving 22795 Asian.[37] Additionally, genetic associations with intraocular pressure (IOP) were derived from a meta-analysis that combined the UKBB, the International Glaucoma Genetics Consortium (IGGC), and The European Prospective Investigation into Cancer- Norfolk (EPIC-Norfolk), including 139555 European.[38]

Summary data for the association between SNPs and stroke was extracted from the MEGASTROKE consortium, encompassing up to 521612 individuals, including 446696 European, 1557 Hispanic or Latin American, 17953 African, and 55406 Asian participants.[39] In addition, we obtained summary statistics for the association between SNPs and ischemic stroke from BBJ, involving 210054 Asian participants.[40] Detailed definition criteria for glaucoma and stroke cases were described in the original publications. The descriptive characteristics of the included studies are shown in Table 1.

2.3. Selection of SNPs

Genetic instruments associated with exposures that reached genome-wide significance ($P < 5 \times 10^{-8}$) were obtained from genome-wide association studies described above. For each selected SNP, we initially assessed its strong association with the exposure using the *F*-statistic. A SNP with an *F*-statistic greater than 10 was supposed to be a strong instrument.[41] After excluding weak instruments, we further pruned index SNPs for linkage disequilibrium ($R^2 > 0.01$ and clump distance <10000 kb) based on the LDlink online tool (https://ldlink.nci.nih.gov). To ensure that the selected SNPs were solely linked with the outcomes via the exposure, we also checked for pleiotropy. We excluded SNPs with potential pleiotropic associations with the outcome, defined by an outcome association *P* value below the genome-wide suggestive significance level of 1×10^{-5}. As previous large population-based studies have demonstrated associations between glaucoma and factors such as body mass index,[42] diabetes,[43] hypertension,[44] and dyslipidemia,[44] all of which are associated with strokes,[45] metabolic-related traits may serve as potential pleiotropic confounders. Therefore, we further checked whether the selected instruments were associated with glucolipid metabolism (including diabetes, dyslipidemia, and glycemic/lipid traits), blood pressure (including hypertension) or body mass index using PhenoScanner (www.phenoscanner.medschl.cam.ac.uk). Totally, we obtained 46 SNPs for glaucoma, 11 SNPs for POAG, 8 SNPs for PACG in the European population. We selected 11 SNPs for POAG in the Asian population as genetic instruments. Additionally, we obtained 15 SNPs for IOP. For stroke, we identified 16 SNPs for AS, 17 SNPs for AIS, 6 SNPs for LAS, and 3 SNPs for CES in the European population as genetic instruments, respectively. Detailed information and potential metabolic-related confounders are provided in Supplemental Tables S1–S4.

2.4. Statistical analysis

In the primary analysis, Wald estimates for each SNP were calculated by dividing the estimate for the SNP on the outcome by the estimate for the SNP on the exposure.[46] Standard errors were obtained using the Delta method.[47] Subsequently, an inverse-variance weighted (IVW) meta-analysis for all instrument SNPs was performed to obtain the overall MR estimate.[41]

Sensitivity analyses were performed by omitting SNPs associated with metabolic factors and calculating a pooled estimate for the remaining SNPs to evaluate whether the results were affected markedly. We also utilized the weighted median and MR-Egger methods to further assess and account for potential bias due to possible pleiotropy.[48,49] The weighted median method is robust for handling invalid instruments and can provide accurate estimates as long as SNPs accounting for at least 50% of the weight are valid instruments.[48] The MR-Egger method is based on the assumption that pleiotropic associations are independent of genetic associations with the exposure. A non-null MR-Egger intercept

Table 1
Summary of data sets used in the study.

Traits	Data set	Sample	Case/control (% of cases)	Females (%)	Mean (SD) age (years)
Glaucoma	GERA&UKBB	214102 European, 5189 Hispanic or Latin American, 6950 African, 10490 Asian, 3571 other mixed ancestry	12315/227987 (5.1%)	55.6%	61.4 (11.1)
POAG	GERA	51901 European, 5189 Hispanic or Latin American, 1847 African, 4475 Asian	4986/58426 (7.9%)	59.7%	70.5 (13.0)
PACG	PACG case-control collections enrolled from 15 countries	5516 European, 20938 Asian	6525/19929 (24.7%)	NA	NA
HTG	NEIGHBORHOOD	33365 European	1868/31497 (5.6%)	89.4%	56.3 (9.4)
NTG	NEIGHBORHOOD	9275 European	725/8550 (7.8%)	75.0%	59.3 (12.1)
POAG	BBJ&J-MICC&JPHC	22795 Asian	3980/18815 (17.5%)	57.0%	56.6 (10.7)
IOP	UKBB&IGGC&EPIC-Norfolk	139555 European	–	NA	NA
AS	MEGASTROKE	446696 European, 1557 Hispanic or Latin American, 17953 African, 55406 Asian	67162/454450 (12.9%)	NA	NA
AIS	MEGASTROKE	440328 European, 1247 Hispanic or Latin American, 17953 African, 55263 Asian	60341/454450 (11.7%)	NA	NA
LAS	MEGASTROKE	301663 European, 733 Hispanic or Latin American, 12671 African, 37250 Asian	6688/345629 (1.9%)	NA	NA
SVS	MEGASTROKE	348946 European, 778 Hispanic or Latin American, 13106 African, 40779 Asian	11710/391899 (2.9%)	NA	NA
CES	MEGASTROKE	362661 European, 791 Hispanic or Latin American, 12826 African, 36535 Asian	9006/403807 (2.2%)	NA	NA
IS	BBJ	210054 Asian	17671/192383 (8.4%)	48.3%	62.0 (13.8)

Note: AS, any stroke; AIS, any ischemic stroke; BBJ, Biobank Japan; CES, cardioembolic stroke; EPIC-Norfolk, The European Prospective Investigation into Cancer-Norfolk; GERA, the Genetic Epidemiology Research in Adult Health and Aging; HTG, high-tension glaucoma; IGGC, the International Glaucoma Genetics Consortium; IOP, intraocular pressure; IS, ischemic stroke; J-MICC, the Japan Multi-Institutional Collaborative Cohort Study; JPHC, the Japan Public Health Center-based Prospective Study; LAS, large-artery atherosclerotic stroke; NA, not available; NEIGHBORHOOD, the National Eye Institute Glaucoma Human Genetics Collaboration Heritable Overall Operational Database; NTG, normal-tension glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma; SD, standard deviation; SVS, small-vessel stroke; UKBB, UK Biobank.

indicates the directional pleiotropy of instruments.[49] Cochrane's Q value was estimated to assess the heterogeneity among different genetic instruments. For the primary bidirectional MR findings, we also conducted supplementary sensitivity analyses, including leave-one-out analyses and single SNP analyses. Moreover, in instances where heterogeneity of genetic instruments or directional pleiotropy was identified, we employed the MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) method to address pleiotropy by removing outliers.

All statistical analyses were conducted using the "Mendelian Randomization", "TwoSampleMR", and "MR-PRESSO" packages in the statistical program R (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). The threshold of $P < 0.05$ was used to determine statistical significance throughout our study.

3. Results

3.1. Effect of glaucoma on stroke

The relationship between glaucoma and the risk of each stroke subtype is depicted graphically in Fig. 1. Our MR analyses, reported as the odds ratio (OR) of stroke per unit increase in log odds of glaucoma, did not identify any significant association of glaucoma with AS (OR = 1.00, 95% confidence interval [CI]: 0.97–1.03, $P = 0.96$), AIS (OR = 1.00, 95% CI: 0.97–1.03, $P = 0.97$), LAS (OR = 1.02, 95% CI: 0.95–1.10, $P = 0.54$), SVS (OR = 0.97, 95% CI: 0.92–1.03, $P = 0.34$), or CES (OR = 0.94, 95% CI: 0.88–1.00, $P = 0.06$) using the IVW method (Fig. 1A). Subsequent single SNP analyses and leave-one-out analyses revealed that no single SNP drove these results, with the exception of the association between glaucoma and CES (Supplemental Fig. S1). Notably, the further MR-PRESSO analysis identified no outlier for that association.

We conducted further sensitivity analyses by omitting SNPs associated with metabolic factors to mitigate potential pleiotropic effects. The removal of these instrumental variables did not lead to a substantial change in the non-significant causal effect (Fig. 1B). In addition, the estimates from the weighted median and MR-Egger method yielded similar results to the IVW estimates, albeit with wider CIs (Fig. 1). Glaucoma was associated with higher risk of LAS in an analysis using the MR-Egger method. However, the corresponding MR-Egger intercept indicated directional pleiotropy (Intercept $P = 0.04$). Following removal of the outlier, association pattern between glaucoma and LAS remained stable (OR = 0.99, 95% CI: 0.92–1.05, $P = 0.67$, P for MR-PRESSO distortion test = 0.19).

3.2. Effect of glaucoma subtypes on stroke

Since the etiologies and mechanisms for glaucoma subtypes are different, we conducted extensive sensitivity analyses by stratifying glaucoma subtypes to validate our findings. Consistent with our main results, both POAG and PACG were not associated with stroke (Fig. 2A and B). Adjustment for metabolic-related traits (Fig. 2C and D) and complementary sensitivity analyses, conducted the weighted median and MR-Egger methods, did not substantially change the estimates, supporting the robustness of our results. The results of the MR-Egger intercept also ruled out the possible influence of directional pleiotropy (Fig. 2).

3.3. Ethnicity stratified analyses in Asian population

Given that most of the previously reported glaucoma-stroke associations were observed in Asians, we also conducted two-sample MR analyses using POAG as the exposure and ischemic stroke as the outcome in the Asian population. Our results did not support a causal effect of POAG on ischemic stroke risk, with or without adjustment for metabolic-related traits (Fig. 3). The MR-Egger intercepts did not differ from the null, indicating no apparent directional pleiotropy.

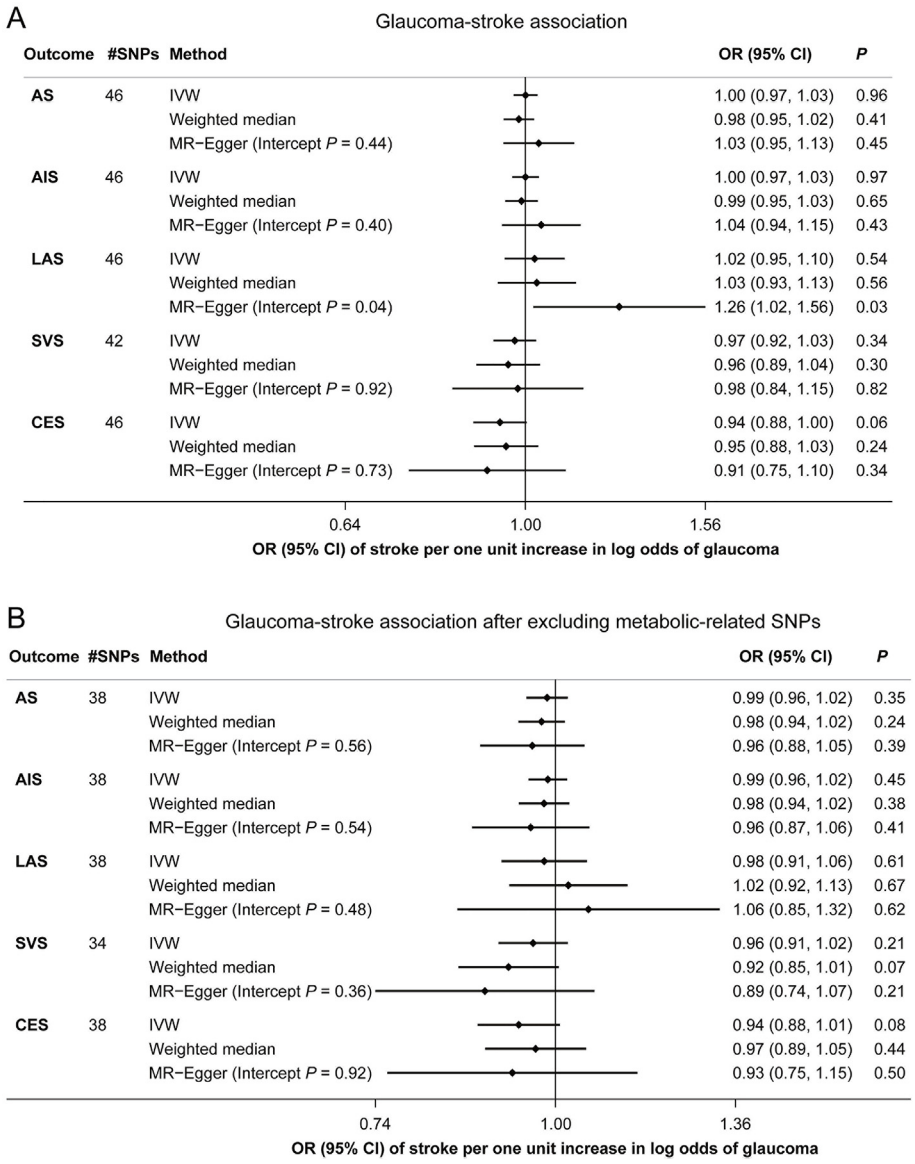


Fig. 1. MR analysis of the effect of glaucoma on stroke without (A) and with (B) adjustment for metabolic-related traits. Effects are shown as OR of stroke per unit increase in the log odds of glaucoma. Metabolic-related traits include glucolipid metabolism, blood pressure, and body mass index. AS, any stroke; AIS, any ischemic stroke; CES, cardioembolic stroke; CI, confidence interval; IVW, inverse-variance weighted; LAS, large-artery atherosclerotic stroke; MR, mendelian randomization; OR, odds ratio; SNP, single-nucleotide polymorphism; SVS, small-vessel stroke.

3.4. Effect of IOP on stroke

Elevated IOP stands as a significant risk factor for glaucoma. In light of this, we conducted meticulous MR analyses to investigate the potential causal link between IOP and the risk of strokes. Our findings failed to substantiate a causal effect of IOP on the risk of stroke and its various subtypes, irrespective of whether adjustments were made for metabolic-related traits (Supplemental Fig. S2). These outcomes found support in both the weighted median model and the MR-Egger model, reinforcing the robustness of our results.

3.5. Reverse MR analysis: effect of stroke on glaucoma

Since only one SNP associated with SVS was available, the association of SVS with glaucoma was not investigated in the reverse MR analysis. In the main analysis, there was no evidence for a causal effect of the genetic risk of AS (OR = 0.95, 95% CI: 0.79–1.13, $P = 0.55$), AIS (OR = 0.97, 95% CI: 0.84–1.12, $P = 0.64$), LAS (OR = 1.00, 95% CI: 0.92–1.09, $P = 0.96$), or CES (OR = 0.96, 95% CI: 0.88–1.04, $P = 0.31$) on glaucoma using the IVW method (Fig. 4A). Additionally, single SNP analyses and leave-one-out analyses suggested that the estimated association is not substantially affected by any single SNP (Supplemental Fig. S3).

In the sensitivity analyses, we did not perform MR analysis on the association of CES with glaucoma since only two SNPs remained available after we excluded rs12932445, which was related to body mass index. Similarly, no evidence of any significant causal effect was found (Fig. 4B). The weighted median and MR-Egger methods produced similar effect estimates (Fig. 4). There was no indication of directional pleiotropy except in the association of AIS with glaucoma (MR-Egger Intercept $P = 0.04$). Furthermore, MR-PRESSO analysis did not identify any outlier SNP.

4. Discussion

In this study, we investigated a potential causal relationship between glaucoma and stroke risk using a series of complementary MR analyses. To minimize the likelihood of confounding bias due to a common data structure, we utilized two different samples for exposure and outcome. Our study encompassed multi-ethnic large-scale genome-wide association studies, including up to 67162 stroke cases and 454450 controls from the MEGASTROKE consortium; 17671 Asian ischemic stroke cases and 182383 Asian controls from the BBJ; as well as 12315 glaucoma cases and 227987 controls from the GERA cohort and the UKBB, of which 4986 POAG cases and 58426 controls were from the GERA cohort; 6525

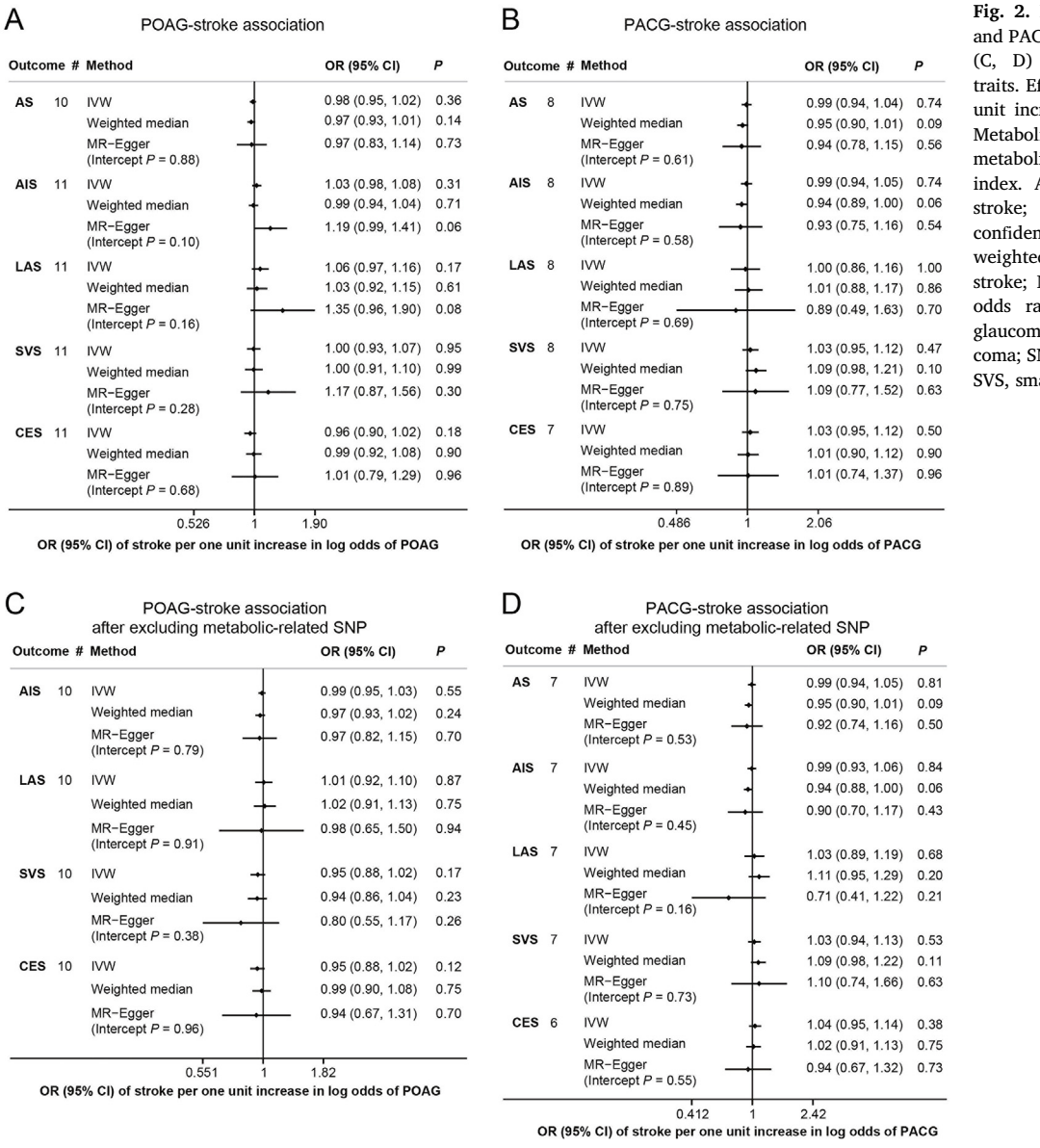


Fig. 2. MR analysis of the effect of POAG and PACG on stroke without (A, B) and with (C, D) adjustment for metabolic-related traits. Effects are shown as OR of stroke per unit increase in the log odds of glaucoma. Metabolic-related traits include glucolipid metabolism, blood pressure, and body mass index. AS, any stroke; AIS, any ischemic stroke; CES, cardioembolic stroke; CI, confidence interval; IVW, inverse-variance weighted; LAS, large-artery atherosclerotic stroke; MR, mendelian randomization; OR, odds ratio; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma; SNP, single-nucleotide polymorphism; SVS, small-vessel stroke.

PACG cases and 19929 controls from the PACG case-control collections; 3980 Asian POAG cases and 18815 Asian controls from the BBJ, the J-MICC study and the JPHC study. Although previous observational studies have reported a significant association between glaucoma and the incidence of stroke,[13–19] our MR analyses found no evidence for a causal role of glaucoma and its subtypes in the risk of AS, AIS, LAS, SVS, or CES. These findings remained robust after adjusting for metabolic-related traits and were consistent in both the European and Asian populations. Furthermore, reverse MR analyses did not identify any significant effect of any stroke subtype (AS, AIS, LAS, or CES) on glaucoma development.

The association between glaucoma and stroke has been debated over recent decades. A prospective cohort study by Ho et al. found that patients with OAG had significantly more strokes over a period of five years, independent of other major risk factors for stroke.[13] Similar results were reported soon after in a different population by Dustin and Curtis. However, they questioned the reasonableness of the suspected association of OAG with stroke and suggested that the relationship deserves further scrutiny, especially in populations of various races.[19] Although some population-based, longitudinal observational studies have reported an increase stroke risk in patients with glaucoma,[13,15,16] conflicting findings have been presented from time to time. An observational cross-sectional study of 50 patients with POAG reported that POAG was associated with stroke and blood pressure; however, these associations did not reach statistical significance.[50] In a population-based cohort study on patients with diabetes, it was found that neither glaucoma nor OAG at baseline was associated with an increased risk of stroke mortality during the 16-year follow-up period, after controlling for other confounding factors.[27] Similarly, another study found no overall statistically significant relationship between OAG and stroke risk after adjusting for selected risk factors.[26] On the other hand, ischemic changes observed via brain magnetic resonance imaging are more common in patients with glaucoma, suggesting a potential relationship between vascular insufficiency in the central nervous system and the pathogenesis of glaucoma.[24,25,51] Atherosclerotic cerebrovascular disease is further reported as a risk factor for a glaucomatous appearance in the optic disc. Symptomatic atherosclerosis involving the brain vasculature may also affect the eye and lead to glaucoma, proposing a reverse causal effect of cerebrovascular disease on the incidence of glaucoma.[23] Epidemiological studies often suffer from confounding bias and reverse causation due to their observational nature; this may partially explain these contradictory findings. Since the genetic variants represented differences that generally persist throughout adult life, an MR study was developed as a natural

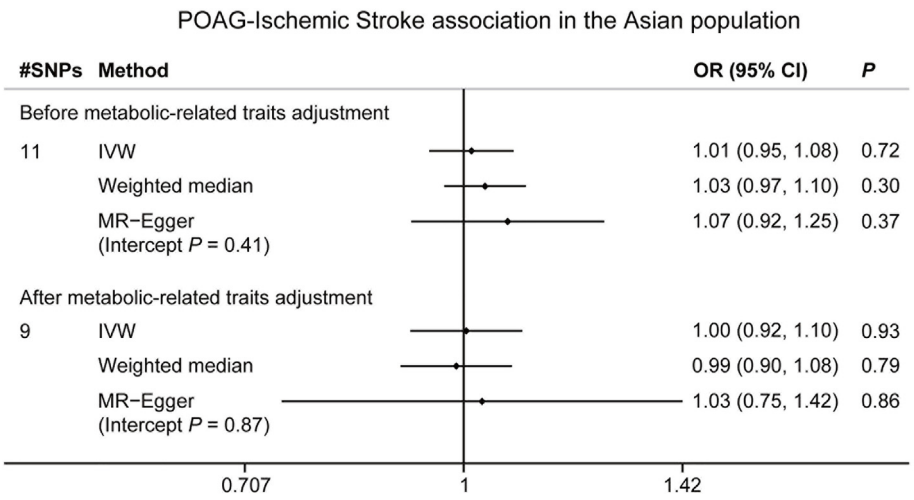


Fig. 3. MR analysis of the effect of POAG on ischemic stroke in the Asian population. Effects are shown as OR of ischemic stroke per unit increase in the log odds of POAG. Metabolic-related traits include glucolipid metabolism, blood pressure, and body mass index. CI, confidence interval; IVW, inverse-variance weighted; MR, mendelian randomization; OR, odds ratio; POAG, primary open-angle glaucoma; SNP, single-nucleotide polymorphism.

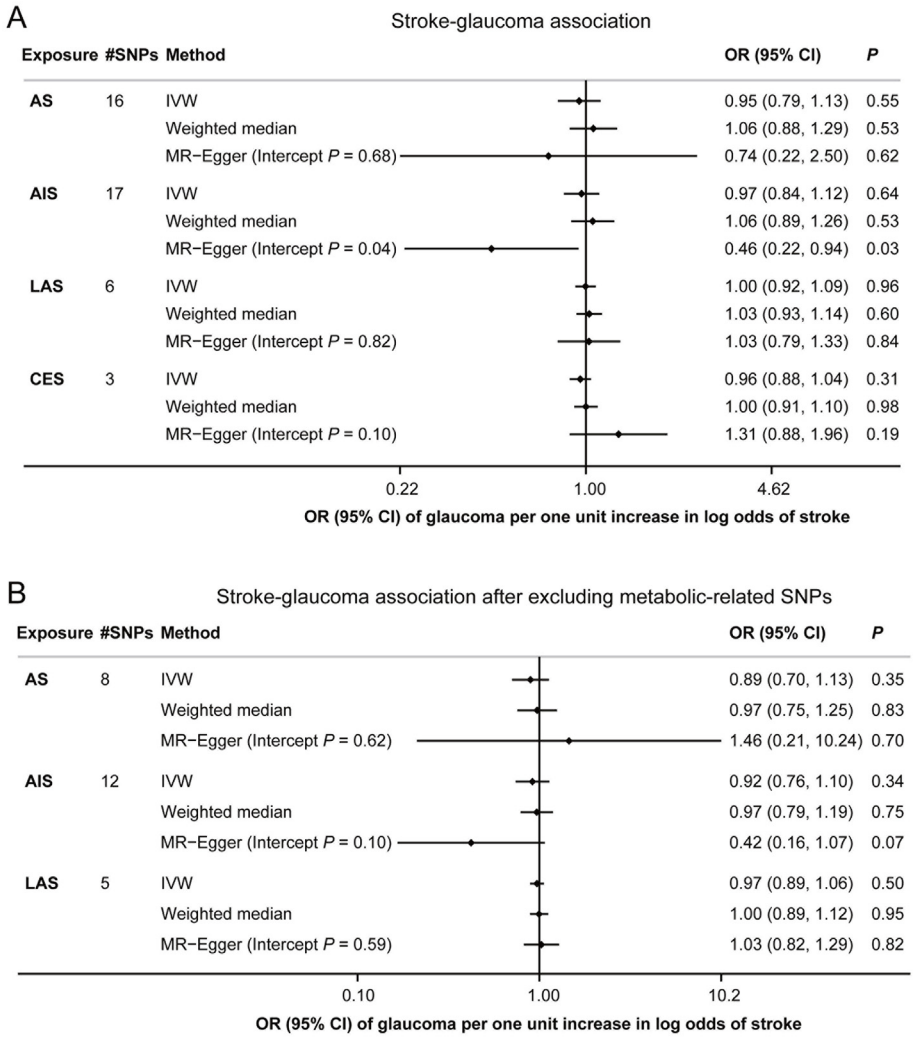


Fig. 4. MR analysis of the effect of stroke on glaucoma without (A) and with (B) adjustment for metabolic-related traits. Effects are shown as OR of glaucoma per unit increase in the log odds of stroke. Metabolic-related traits include glucolipid metabolism, blood pressure, and body mass index. AS, any stroke; AIS, any ischemic stroke; CES, cardioembolic stroke; CI, confidence interval; IVW, inverse-variance weighted; LAS, large-artery atherosclerotic stroke; MR, mendelian randomization; OR, odds ratio; SNP, single-nucleotide polymorphism.

randomized controlled trial, and its estimates reflect the lifelong effect of glaucoma or stroke. Compared to traditional randomized trials, MR is a cost-effective way to obtain unbiased causal effect estimates without any exposures for humans or animals; it also does not require long follow-up durations. In our results, bidirectional MR estimates showed no causal relationship between glaucoma and stroke.

According to the vascular theory, blood vessel disease leads to vascular dysregulation and defective autoregulation of ocular blood flow. These, in turn, lead to unstable oxygen supply and oxidative stress, further resulting in ischemic optic nerve damage and glaucomatous optic neuropathy.[11,52] On the other hand, because blood vessels in the optic nerve and retina share a common embryonic origin, along with similar anatomy, vasculature, blood barrier, and physiological characteristics as cerebral vessels, pathological changes in the vessels of the optic nerve may reflect similar changes in cerebral vessels.[53,54] Both of these factors may result in clinical and biological relevance between the development of glaucoma, especially for OAG, which is associated with abnormal ocular blood flow parameters, and stroke, a representative vascular disease associated with abnormal cerebral vasculature. Previously observed associations between glaucoma and stroke were more common observed for POAG subtypes and among the Asian population. However, our further stratified results did not support a causal effect after stratification of POAG on stroke incidence, with or without adjustment for metabolic-related traits, especially on the risk of ischemic stroke in the Asian population. This warrants further clarification in other ethnicities.

Biologically, the association between glaucoma and the broad spectrum of stroke diagnoses warrants further consideration. Hypertension and diabetes are well-known risk factors for stroke.[55] Meanwhile, observational studies have suggested that hypertension and diabetes may increase the risk of glaucoma.[56,57] Chronic kidney disease, atrial fibrillation, and many other common risk factors for both of these two diseases have been recognized in previous studies,[58–61] indicating interaction and interference among these comorbid conditions. In addition, although glaucoma and stroke share common pathophysiological mechanisms, especially regarding vascular abnormalities,[62–64] the hypothesis that vascular diseases arising in other organs may contribute to the pathogenesis of glaucoma is controversial.[65] Lastly, stroke conditions encompass a variety of different neurovascular disorders, from transient ischemic attack to subarachnoid hemorrhage. These disorders usually involve different disease pathways,[19] suggesting that reaching a conclusion about the predictive power of glaucoma on stroke incidence is challenging.

The present study has several potential limitations that deserve comment. First, the validity of MR findings depends on the crucial assumptions that the genetic predictors are strongly associated with the exposure and affect the outcome only through intermediate phenotypes of interest and not through others pathways (i.e., that no pleiotropy exists). To satisfy these assumptions, we selected multiple independent SNPs that are significantly associated with glaucoma or stroke according to previously published genome-wide association studies. Moreover, since metabolic-related traits, including diabetes, hypertension, and dyslipidemia, are common risk factors for metabolic syndrome and have been suggested as potential confounders in the glaucoma-stroke relationship,[15,18,26,55,66,67] we also used different MR approaches and adjusted our findings for metabolic-related traits with these relevant markers. Although the MR-Egger intercepts in the glaucoma-LAS and AIS-glaucoma associations suggested possible directional pleiotropy, they were no longer significant after adjustment for metabolic-related traits. The consistency of our findings indicates that unknown pleiotropy is less likely. Second, the data on glaucoma in the UKBB relied on patient reports or recall. Thus, possible misdiagnosis and conditions such as mild sufferers remaining undiagnosed should be considered when interpreting the results. Third, the use of publicly available summary-level data hinders subgroup analyses by sex, age, and other demographic information. Therefore, further MR studies with individual-level data are warranted. Fourth, Sample overlap existed because both Asian datasets included BBJ.

5. Conclusions

In conclusion, our large population-based MR study did not support a causal effect of glaucoma or its subtypes on stroke risk. Additional reverse MR analyses also showed no evidence for an association of diverse stroke with glaucoma. Our results suggested that the correlation between glaucoma management and stroke risk prevention should be carefully evaluated in future studies. In turn, stroke diagnosis should not be simply applied to glaucoma risk prediction.

Study approval

Studies included in our research have received ethical approval from relevant institutional review boards. According to the institutional review board of the Second Affiliated Hospital of Zhejiang University School of Medicine, as we used publicly available summary-level data from the published genome-wide meta-analysis, no additional ethical approval was required.

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: KW, XL (Xueqi Lin), KY; Data collection: KW, XL (Xueqi Lin), SS, DC, XL (Xin Liu); Analysis and interpretation of results: KW, XL (Xueqi Lin), SS, DC; Drafting the manuscript: KW, XL (Xueqi Lin), XL (Xin Liu); All authors reviewed the results and approved the final version of the manuscript.

Funding

This work was supported by grants from the Program of National Natural Science Foundation (81870641, 82070939, 82201242), Strategic Priority Research Program of the Chinese Academy of Sciences (XDA16010304) and Key Research and Development Project of Zhejiang Province (2020C03035).

Editorship disclosure

Given his role as Editor-in-Chief, Ke Yao had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Prof. Andrzej Grzybowski.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank all the investigators of the GERA cohort, the UKBB, the included PACG case-control collections, the BBJ, the J-MICC study, the JPHC study, and the MEGASTROKE consortium for providing the data publicly.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aopr.2024.04.003.

References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. *Circulation*. 2011;123(4):e18–e209. https://doi.org/10.1161/CIR.0b013e3182009701.
2. Esenwa C, Gutierrez J. Secondary stroke prevention: challenges and solutions. *Vasc Health Risk Manag*. 2015;11:437–450. https://doi.org/10.2147/VHRM.S63791.
3. Rowe FJ, et al. Vision in Stroke cohort: profile overview of visual impairment. *Brain Behav*. 2017;7(11):e00771. https://doi.org/10.1002/brb3.771.
4. Rowe FJ, Hepworth LR, Howard C, et al. High incidence and prevalence of visual problems after acute stroke: an epidemiology study with implications for service

delivery. *PLoS One*. 2019;14(3):e0213035. https://doi.org/10.1371/journal.pone.0213035.
5. Smith TM, Pappadis MR, Krishnan S, et al. Stroke survivor and caregiver perspectives on post-stroke visual concerns and long-term consequences. *Behav Neurol*. 2018; 2018:1463429. https://doi.org/10.1155/2018/1463429.
6. Chou R, Dana T, Bougatsos C, et al. Screening for impaired visual acuity in older adults: updated evidence report and systematic review for the US preventive services task force. *JAMA*. 2016;315(9):915–933. https://doi.org/10.1001/jama.2016.0783.
7. Hreha KP, Fisher SR, Reistetter TA, et al. Use of the ICD-10 vision codes to study ocular conditions in Medicare beneficiaries with stroke. *BMC Health Serv Res*. 2020; 20(1):628. https://doi.org/10.1186/s12913-020-05484-z.
8. Jonas JB, Aung T, Bourne RR. *Lancet*. 2017;390(10108):2183–2193. https://doi.org/10.1016/S0140-6736(17)31469-1.
9. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. 2014;311(18):1901–1911. https://doi.org/10.1001/jama.2014.3192.
10. Fechtner RD, Weinreb RN. Mechanisms of optic nerve damage in primary open angle glaucoma. *Surv Ophthalmol*. 1994;39(1):23–42. https://doi.org/10.1016/s0039-6257(05)80042-6.
11. Yanagi M, Kawasaki R, Wang JJ, et al. Vascular risk factors in glaucoma: a review. *Clin Exp Ophthalmol*. 2011;39(3):252–258. https://doi.org/10.1111/j.1442-9071.2010.02455.x.
12. Guzik A, Bushnell C. Stroke epidemiology and risk factor management. *Continuum*. 2017;23(1, Cerebrovascular Disease):15–39. https://doi.org/10.1212/con.0000000000000416.
13. Ho JD, Hu CC, Lin HC. Open-angle glaucoma and the risk of stroke development: a 5-year population-based follow-up study. *Stroke*. 2009;40(8):2685–2690. https://doi.org/10.1161/strokeaha.109.554642.
14. Lee MS, Kuo LL, Tan EC, et al. Is normal-tension glaucoma a risk factor for stroke?-A 10-year follow-up study. *PLoS One*. 2017;12(6):e0179307. https://doi.org/10.1371/journal.pone.0179307.
15. Lee SH, Kim GA, Lee W, et al. Vascular and metabolic comorbidities in open-angle glaucoma with low- and high-teen intraocular pressure: a cross-sectional study from South Korea. *Acta Ophthalmol*. 2017;95(7):e564–e574. https://doi.org/10.1111/aos.13487.
16. Rim TH, Lee SY, Bae HW, et al. Increased stroke risk among patients with open-angle glaucoma: a 10-year follow-up cohort study. *Br J Ophthalmol*. 2018;102(3):338–343. https://doi.org/10.1136/bjophthalmol-2017-310415.
17. Su CW, Chang YC, Lin CL, et al. Association of neovascular glaucoma with risk of stroke: a population-based cohort study. *J Ophthalmol*. 2017;2017:1851568. https://doi.org/10.1155/2017/1851568.
18. Lin HC, Chien CW, Hu CC, et al. Comparison of comorbid conditions between open-angle glaucoma patients and a control cohort: a case-control study. *Ophthalmology*. 2010;117(11):2088–2095. https://doi.org/10.1016/j.ophtha.2010.03.003.
19. French DD, Margo CE. Open angle glaucoma and stroke. *Ophthalmology*. 2010; 117(8):1653–1654. https://doi.org/10.1016/j.ophtha.2010.03.016.
20. Leung DY, Tham CC, Li FC, et al. Silent cerebral infarct and visual field progression in newly diagnosed normal-tension glaucoma: a cohort study. *Ophthalmology*. 2009; 116(7):1250–1256. https://doi.org/10.1016/j.ophtha.2009.02.003.
21. Schoemann J, Engelhorn T, Waerntges S, et al. Cerebral microinfarcts in primary open-angle glaucoma correlated with DTI-derived integrity of optic radiation. *Invest Ophthalmol Vis Sci*. 2014;55(11):7241–7247. https://doi.org/10.1167/iovs.14-14919.
22. Flammer J, Orgül S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res*. 2002;21(4):359–393. https://doi.org/10.1016/s1350-9462(02)00008-3.
23. Güngör IU, Güngör L, Ozarslan Y, et al. Is symptomatic atherosclerotic cerebrovascular disease a risk factor for normal-tension glaucoma? *Med Princ Pract : international journal of the Kuwait University, Health Science Centre*. 2011;20(3): 220–224. https://doi.org/10.1159/000323596.
24. Ong K, Farinelli A, Billson F, et al. Comparative study of brain magnetic resonance imaging findings in patients with low-tension glaucoma and control subjects. *Ophthalmology*. 1995;102(11):1632–1638. https://doi.org/10.1016/s0161-6420(95)30816-0.
25. Suzuki J, Tomidokoro A, Araie M, et al. Visual field damage in normal-tension glaucoma patients with or without ischemic changes in cerebral magnetic resonance imaging. *Jpn J Ophthalmol*. 2004;48(4):340–344. https://doi.org/10.1007/s10384-004-0072-0.
26. Lee WJ, Jeoung JW, Na KI, et al. Relationship between open-angle glaucoma and stroke: a 2010 to 2012 Korea National Health and Nutrition Examination Survey. *J Glaucoma*. 2018;27(1):22–27. https://doi.org/10.1097/ijg.0000000000000829.
27. Klein R, Klein BE, Moss SE, et al. Association of ocular disease and mortality in a diabetic population. *Arch Ophthalmol*. 1999;117(11):1487–1495. https://doi.org/10.1001/archopht.117.11.1487.
28. Robinson PC, Choi HK, Do R, et al. Insight into rheumatological cause and effect through the use of Mendelian randomization. *Nat Rev Rheumatol*. 2016;12(8): 486–496. https://doi.org/10.1038/nrrheum.2016.102.
29. Hysi PG, Khawaja AP, Menni C, et al. Ascorbic acid metabolites are involved in intraocular pressure control in the general population. *Redox Biol*. 2019;20:349–353. https://doi.org/10.1016/j.redox.2018.10.004.
30. Shen L, Walter S, Melles RB, et al. Diabetes pathology and risk of primary open-angle glaucoma: evaluating causal mechanisms by using genetic information. *Am J Epidemiol*. 2016;183(2):147–155. https://doi.org/10.1093/aje/kwv204.
31. Hindy G, Engström G, Larsson SC, et al. Role of blood lipids in the development of ischemic stroke and its subtypes: a mendelian randomization study. *Stroke*. 2018; 49(4):820–827. https://doi.org/10.1161/strokeaha.117.019653.
32. Hopewell JC, Clarke R. Emerging risk factors for stroke: what have we learned from mendelian randomization studies? *Stroke*. 2016;47(6):1673–1678. https://doi.org/10.1161/strokeaha.115.010646.
33. Larsson SC, Scott RA, Traylor M, et al. Type 2 diabetes, glucose, insulin, BMI, and ischemic stroke subtypes: mendelian randomization study. *Neurology*. 2017;89(5): 454–460. https://doi.org/10.1212/wnl.0000000000004173.
34. Yang F, Chen S, Qu Z, et al. Genetic liability to sedentary behavior in relation to stroke, its subtypes and neurodegenerative diseases: a mendelian randomization study. *Front Aging Neurosci*. 2021;13:757388. https://doi.org/10.3389/fnagi.2021.757388.
35. Choquet H, Paylakhi S, Kneeland SC, et al. A multiethnic genome-wide association study of primary open-angle glaucoma identifies novel risk loci. *Nat Commun*. 2018; 9(1):2278. https://doi.org/10.1038/s41467-018-04555-4.
36. Khor CC, Do T, Jia H, et al. Genome-wide association study identifies five new susceptibility loci for primary angle closure glaucoma. *Nat Genet*. 2016;48(5): 556–562. https://doi.org/10.1038/ng.3540.
37. Shiga Y, Akiyama M, Nishiguchi KM, et al. Genome-wide association study identifies seven novel susceptibility loci for primary open-angle glaucoma. *Hum Mol Genet*. 2018;27(8):1486–1496. https://doi.org/10.1093/hmg/ddy053.
38. Khawaja AP, Cooke Bailey JN, Wareham NJ, et al. Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma. *Nat Genet*. 2018;50(6):778–782. https://doi.org/10.1038/s41588-018-0126-8.
39. Malik R, Chauhan G, Traylor M, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet*. 2018;50(4):524–537. https://doi.org/10.1038/s41588-018-0058-3.
40. Ishigaki K, Akiyama M, Kanai M, et al. Large-scale genome-wide association study in a Japanese population identifies novel susceptibility loci across different diseases. *Nat Genet*. 2020;52(7):669–679. https://doi.org/10.1038/s41588-020-0640-3.
41. Palmer TM, Lawlor DA, Harbord RM, et al. Using multiple genetic variants as instrumental variables for modifiable risk factors. *Stat Methods Med Res*. 2012;21(3): 223–242. https://doi.org/10.1177/0962280210394459.
42. Lin SC, Pasquale LR, Singh K, et al. The association between body mass index and open-angle glaucoma in a South Korean population-based sample. *J Glaucoma*. 2018; 27(3):239–245. https://doi.org/10.1097/IJG.0000000000000867.
43. Chopra V, Varma R, Francis BA, et al. Type 2 diabetes mellitus and the risk of open-angle glaucoma the Los Angeles Latino Eye Study. *Ophthalmology*. 2008;115(2): 227–232 e221. https://doi.org/10.1016/j.ophtha.2007.04.049.
44. Newman-Casey PA, Talwar N, Nan B, et al. The relationship between components of metabolic syndrome and open-angle glaucoma. *Ophthalmology*. 2011;118(7): 1318–1326. https://doi.org/10.1016/j.ophtha.2010.11.022.
45. Elkind MS, Sacco RL. Stroke risk factors and stroke prevention. *Semin Neurol*. 1998; 18(4):429–440. https://doi.org/10.1055/s-2008-1040896.
46. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7): 658–665. https://doi.org/10.1002/gepi.21758.
47. Thompson JR, Minelli C, Del Greco MF. Mendelian randomization using public data from genetic consortia. *Int J Biostat*. 2016;12(2). https://doi.org/10.1515/ijb-2015-0074.
48. Bowden J, Davey Smith G, Haycock PC, et al. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314. https://doi.org/10.1002/gepi.21965.
49. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol*. 2017;32(5):377–389. https://doi.org/10.1007/s10654-017-0255-x.
50. Belzunce A, Casellas M. Vascular risk factors in primary open angle glaucoma. *An Sist Sanit Navar*. 2004;27(3):335–344. https://doi.org/10.4321/s1137-66272004000500005.
51. Stroman GA, Stewart WC, Golnik KC, et al. Magnetic resonance imaging in patients with low-tension glaucoma. *Arch Ophthalmol*. 1995;113(2):168–172. https://doi.org/10.1001/archopht.1995.01100020050027.
52. Wu X, Konieczka K, Liu X, et al. Role of ocular blood flow in normal tension glaucoma. *Adv Ophthalmol Pract Res*. 2022;2(1):100036. https://doi.org/10.1016/j.aopr.2022.100036.
53. Kumar V. Understanding retinal changes after stroke. *Open J Ophthalmol*. 2017;7(4): 281–292. https://doi.org/10.4236/ojoph.2017.74037.
54. De Silva DA, Manzano JJ, Liu EY, et al. Retinal microvascular changes and subsequent vascular events after ischemic stroke. *Neurology*. 2011;77(9):896–903. https://doi.org/10.1212/WNL.0b013e31822c623b.
55. Sherzai AZ, Elkind MS. Advances in stroke prevention. *Ann N Y Acad Sci*. 2015;1338: 1–15. https://doi.org/10.1111/nyas.12723.
56. Bae HW, Lee N, Lee HS, et al. Systemic hypertension as a risk factor for open-angle glaucoma: a meta-analysis of population-based studies. *PLoS One*. 2014;9(9): e108226. https://doi.org/10.1371/journal.pone.0108226.
57. Zhou M, Wang W, Huang W, et al. Diabetes mellitus as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *PLoS One*. 2014;9(8):e102972. https://doi.org/10.1371/journal.pone.0102972.
58. Masson P, Webster AC, Hong M, et al. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2015;30(7): 1162–1169. https://doi.org/10.1093/ndt/gfv009. official publication of the European Dialysis and Transplant Association - European Renal Association.
59. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114(2):119–125. https://doi.org/10.1161/circulationaha.105.595140.

60. Sanders DS, Mansberger SL. Obstructive sleep apnea and primary open-angle glaucoma. *J Glaucoma*. 2019;28(8):667. https://doi.org/10.1097/ijg.0000000000001304.
61. Wang TJ, Wu CK, Hu CC, et al. Increased risk of co-morbid eye disease in patients with chronic renal failure: a population-based study. *Ophthalmic Epidemiol*. 2012;19(3):137–143. https://doi.org/10.3109/09286586.2012.680531.
62. Mitchell P, Leung H, Wang JJ, et al. Retinal vessel diameter and open-angle glaucoma: the blue mountains eye study. *Ophthalmology*. 2005;112(2):245–250. https://doi.org/10.1016/j.ophtha.2004.08.015.
63. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the atherosclerosis risk in communities study. *Lancet*. 2001;358(9288):1134–1140. https://doi.org/10.1016/s0140-6736(01)06253-5.
64. Lee JY, Yoo C, Park JH, et al. Retinal vessel diameter in young patients with open-angle glaucoma: comparison between high-tension and normal-tension glaucoma. *Acta Ophthalmol*. 2012;90(7):e570–e571. https://doi.org/10.1111/j.1755-3768.2011.02371.x.
65. Bonomi L, Marchini G, Marraffa M, et al. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. *Ophthalmology*. 2000;107(7):1287–1293. https://doi.org/10.1016/s0161-6420(00)00138-x.
66. Kolar P. Risk factors for central and branch retinal vein occlusion: a meta-analysis of published clinical data. *Journal of ophthalmology*. 2014;2014:724780. https://doi.org/10.1155/2014/724780.
67. Tham YC, Cheng CY. Associations between chronic systemic diseases and primary open angle glaucoma: an epidemiological perspective. *Clin Exp Ophthalmol*. 2017;45(1):24–32. https://doi.org/10.1111/ceo.12763.