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The causal effect of glaucoma and diabetic retinopathy: a Mendelian randomization study

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Abstract

Background Previous research showed that there is an important association between glaucoma and diabetic retinopathy (DR). However, the relationship has not been clarified. In this study, we attempted to evaluate it.

Methods We conducted bidirectional Two-sample Mendelian randomization (MR), Multivariable Mendelian randomization (MVMR), and Mediation analysis. The Inverse-variance-weighted method was adopted as the main MR method, supplemented by MR-Egger, weighted median, weighted mode, and simple mode.

Results The results of forward MR analysis suggested that glaucoma [$p = 0.001$, odds ratio (OR) = 1.080] and intraocular pressure (IOP) ($p = 0.019$, OR = 1.100) as risk factors for DR. The reverse MR found that DR was a risk factor for glaucoma ($p = 0.039$, OR = 1.024) and IOP ($p = 0.010$, OR = 1.057). The results of MVMR analysis demonstrated that glaucoma ($p = 0.046$, OR = 1.069) remained an independent risk factor for DR. The bidirectional relationship between glaucoma and DR is mediated by IOP, according to the results of the Two-step MR analysis. Besides, glaucoma contributed to the positive causal link that exists between IOP and DR.

Conclusion The findings demonstrated a reciprocal causal link between glaucoma and DR, with a possible mediating function for IOP. Moreover, glaucoma played an important mediator of IOP as a risk factor for DR. It offers recommendations for the early prevention of both DR and glaucoma.

Keywords Diabetic retinopathy, Mendelian randomization, Glaucoma, Intraocular pressure, Retinal nerve fiber layer

Introduction

As a common complication of diabetes mellitus (DM), diabetic retinopathy (DR) is the leading cause of preventable blindness in adults aged 20–74 years [1]. According to the study, the global prevalence of DR is expected to increase significantly in the future, from approximately 103 million people in 2020 to 161 million people in 2045 [2]. Consequently, it is critical to recognize possible risk factors and manage their contributions to the development of DR.

As the leading cause of irreversible blindness worldwide, Glaucoma is a group of progressive optic neuropathies causing visual deficits, mainly characterized

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by retinal ganglion cells (RGCs) degeneration [3]. The optic nerve consists of a confluence of ganglion cell axonal fibers in the retina that transmit visual signals to the visual center through the optic disc. Glaucoma causes changes in the optic disc which can be manifested as an increased cup-to-disc ratio and defects in the retinal nerve fiber layer (RNFL) [3]. The mainstay of treatment for glaucoma is the reduction of intraocular pressure (IOP) [4]. Understanding the risk factors of glaucoma is the basis of glaucoma prevention.

The burgeoning quantity of studies consistently shows that there is a significant link between DR and glaucoma [5–7]. Despite this, no conclusive evidence has been found to determine whether one condition directly causes the other. Observational designs and small sample sizes predominantly limit the scope of studies. As a result, the ability to make valid causal deductions is hampered, and the studies become exposed to the potential distorting effects of numerous confounding variables. Mendelian randomization (MR) analysis utilizes genetic variation as an instrumental variable (IV) to assess the causal impact of exposure factors on outcomes which minimizes the effect of confounders and reverse causation [8].

To the best of our knowledge, this study is the first to use bidirectional MR to explore the causal association of glaucoma and its associated features with DR and to further investigate these associations by employing the MVMR method to rule out pleiotropy. Moreover, two-step MR was utilized to explore the potential causal relationship of IOP and glaucoma with DR.

Materials and methods

Research design

Single-nucleotide polymorphisms (SNPs) used as genetic IVs in MR analyses must satisfy the following three assumptions: (1) Association: the IVs must be correlated with the exposure; (2) Independence: the IVs must affect the outcome only through the exposure; and (3) Exclusion of restriction: the outcome is affected only through the exposure. The flow of this study and the three hypotheses are shown in Fig. 1.

Data source

Data from genome-wide association studies (GWASs) had previously received ethical consent. Only pooled data were used in this paper, so additional approvals were required. To minimize the influence of ethnicity, we restricted the study population to Europeans.

Data on glaucoma and its characteristics

The glaucoma dataset (ID: ebi-a-GCST90018852) includes 484,979 individuals, including 10,411 cases. Glaucoma occurs as a result of elevated ocular pressure due to obstruction of outflow of atrial fluid. The IOP dataset (ID: ukb-b-12440) contains a sample size of

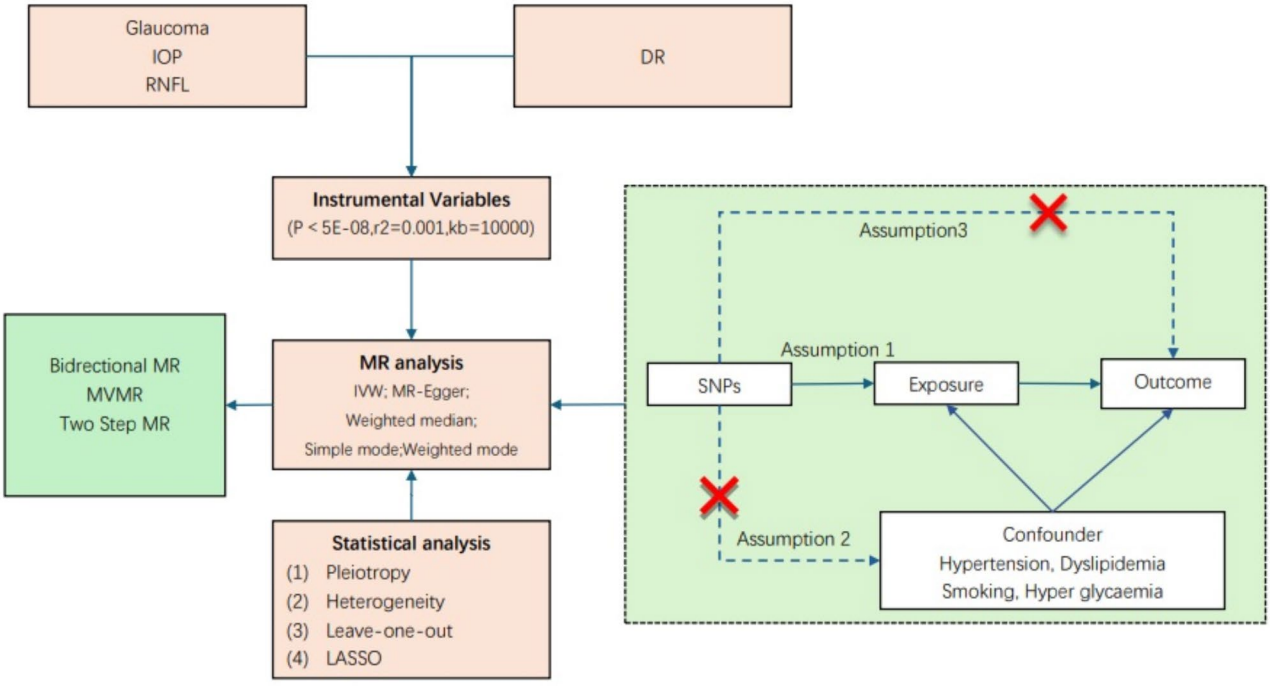

Fig. 1 Flow chart and three assumptions for this MR study. IOP: intraocular pressure; RNFL: retinal nerve fiber layer; DR: diabetic retinopathy; MR: mendelian randomization; MVMR: multivariable mendelian randomization; LASSO: least absolute shrinkage and selection operator; SNPs:single-nucleotide polymorphisms

97,465. The RNFL dataset (ID: ebi-a-GCST90014266) contains a sample size of 31,434. Summary data for glaucoma, IOP, and RNFL were obtained from IEU Open GWAS(http://gwas.mrcieu.ac.uk).

Data on DR

To minimize sample overlap, data for DR (ID: finn-b-DM_RETINOPATHY) were selected from FinnGen (http://www.finngen.fi/en) for a total of 216,666 indivi duals of European ancestry (including 14,584 cases and 20,082 controls) [9]. DR is a chronic pathologic complication associated with diabetes mellitus that results in vision loss or blindness due to retinal damage caused by microaneurysms in the retinal blood vessels, which gradually lead to abnormal blood vessel proliferation, vascular swelling, and fluid leakage.

Selection of IVs

To verify this bidirectional causal relationship between glaucoma, IOP, RNFL, and DR, we screened IVs for these phenotypes. Firstly, to satisfy MR assumptions (Fig. 1), SNPs that were strongly associated with exposure ($p < 5 \times 10^{-8}$) were selected. Secondly, we used clump ($R^2 = 0.001$, kb = 10000) to remove SNPs with substantial linkage disequilibrium to guarantee the independence of SNPs. Thirdly, IVs with F-statistics < 10 were excluded by computing the F-statistic of each SNP, which was calculated by the following equation: $F = R^2 \times (N-2)/(1-R^2)$, where N is the sample size and R^2 is the proportion of explainable variance of the associations between the SNPs and the exposure. The formula for R^2 is $R^2 = \beta^2/(\beta^2 + SE^2 \times N)$, where β is the value of the allele effect and SE is the effect standard error. When the F-statistic > 10, the IV will not be affected by weak instrument bias. Fourthly, SNPs must affect outcomes through exposure rather than other direct pathways. Furthermore, LDlink (https://ldlink.nih.gov/) furnished data sourced from the Catalog. We employed this data to screen out SNPs that harbored risk factors relevant to the outcome variable. Finally, SNPs with ambiguous allele information were excluded using the harmonized function included in the "TwoSampleMR" packages. For all statistical data analysis in this study, we employed the "TwoSampleMR" packages within the R programming environment, specifically version 4.3.2. The selected SNPs are listed in Table 1 of the supplementary material. (Supplementary Material).

Methods of analysis

MR analysis

In this study, five complementary methods were used to estimate the causal relationship between glaucoma, IOP, RNFL, and DR, including inverse-variance weighted (IVW), MR-Egger regression, weighted median, weighted model, and simple model. The IVW was the primary analytical method. Reliable results can be obtained by IVW in the absence of horizontal pleiotropy and heterogeneity [10]. MR-Egger regression can assess the ability of horizontal pleiotropy by the intercept value. Even if as many as half of the SNPs violate horizontal pleiotropy, the weighted median can provide consistent estimates of causal effect [11]. Weighted model and simple model are used as complementary methods for causality evaluation. Finally, we employed the Benjamini-Hochberg false discovery rate (FDR) method to correct for multiple comparisons.

Multivariable Mendelian randomization (MVMR), as a complementary method to MR, was used to further examine the associations between these outcome-related exposures, estimating the independent direct effect of multiple potentially relevant exposures [12]. In addition, we used the least absolute shrinkage and selection operator (LASSO) for feature selection.

LASSO is a penalized regression method designed to enhance the predictive accuracy and interpretability of linear regression models [13]. It achieves this by imposing an absolute value penalty on the regression coefficients, which helps to reduce the number of variables in the model and performs feature selection by setting some coefficients to exactly zero. The regression coefficients indicate the strength of association of each exposure factor with the dependent variable which may be a disease or trait in the LASSO. A positive coefficient signifies a positive association between the exposure and the

Table 1 Bidirectional Mendelian randomization results

Exposure	Outcome	IVs	Cochran Q test		MR-Egger Intercept (*p*)	MR-PRESSO RSSobs(*p*)
			MR-egger(*p*)	IVW(*p*)		
Glaucoma	DR	31	0.748	0.737	0.290	0.739
IOP	DR	86	0.655	0.609	0.118	0.599
RNFL	DR	21	0.753	0.797	0.734	0.805
DR	Glaucoma	13	0.643	0.689	0.547	0.711
DR	IOP	12	0.039	0.016	0.998	0.055
DR	RNFL	11	0.293	0.250	0.250	0.335

IVs: instrumental variables; IVW: Inverse-variance-weighted; MR-PRSSO: MR pleiotropy residual sum outlier; IOP: intraocular pressure; RNFL: retinal nerve fiber layer; DR: diabetic retinopathy

outcome, whereas a negative coefficient indicates a negative association.

Sensitivity analysis

Sensitivity tests, including Cochran's Q test, MR-Egger intercept, MR pleiotropy residual sum outlier (MR-PRSSO), and leave-one-out analysis, were performed to test for heterogeneity, horizontal pleiotropy, and stability of the analyzed results. Cochran's Q test was used to assess the heterogeneity of individual SNPs. MR-PRESSO global test detects overall horizontal pleiotropy and removes outliers in IVW linear regression by outlier testing to provide corrected MR results [14].

Result

Bidirectional MR

IVW genetic analysis revealed that with DR as the outcome, glaucoma [Odds Ratio(OR) = 1.080, 95% confidence interval (CI) = 1.029,1.133; $p = 0.001$, FDR-corrected $p = 0.006$] and IOP (OR = 1.100, 95% CI = 1.015, 1.191; $p = 0.019$, FDR-corrected $p = 0.038$) were positively correlated with DR, while RNFL (OR = 0.996, 95% CI = 0.975, 1.018; $p = 0.756$, FDR-corrected $p = 0.756$) showed no significant correlation.

When DR was the exposure, it was positively correlated with IOP (OR = 1.057, 95% CI = 1.013, 1.104; $p = 0.010$, FDR-corrected $p = 0.030$) and glaucoma (OR = 1.024, 95% CI = 1.001, 1.047; $p = 0.039$, FDR-corrected $p = 0.058$), but RNFL (OR = 1.103, 95% CI = 0.923, 1.319; $p = 0.277$, FDR-corrected $p = 0.332$) had no significant correlation with DR. The results of IVW analyses are shown in Fig. 2. The causal relationship between the exposure and the outcome of this bidirectional MR study is represented in Fig. 3.

In this study, all Cochran's Q tests except DR-IOP p-values > 0.05, which suggests that there is no heterogeneity between exposures and outcomes. The p-values derived from all MR-Egger intercept tests and MR-PRESSO global test were > 0.05, which suggests that there is no horizontal pleiotropy (Table 1). Finally, the leave-one-out analysis confirmed that the causal relationship between exposures and outcomes was not due to a specific SNP (Supplementary Material). In summary, the results are reliable.

MVMR analysis

Since MR indicated a significant correlation between DR and glaucoma as well as IOP, but not with RNFL, we performed MVMR analysis to assess their potential joint involvement in the relationship with DR. Using glaucoma and IOP as exposures, the results of MVMR-IVW analysis demonstrated a positive causal relationship only between DR and glaucoma (OR = 1.069, 95%CI = 1.001,1.142; $p = 0.046$), whereas there was no statistically significant causal link between IOP (OR = 1.036, 95%CI = 0.993–1.160; $p = 0.536$) and DR when excluding glaucoma. MVMR-Egger also confirmed glaucoma as an independent risk for DR (Table 2).

Furthermore, the idea that there was no substantial heterogeneity across the SNPs was supported by the fact that Cochran's Q test P-value was greater than 0.05. The lack of significant heterogeneity among SNPs was indicated by a Cochran's Q test p-values > 0.05. LASSO results showed positive regression coefficients for glaucoma (0.063) and IOP (0.029), suggesting a positive correlation with DR. The larger coefficient for glaucoma implies a potentially stronger association with DR.

Mediation analysis

We conducted mediation analysis via a two-step MR method. In the first step, we removed SNPs related to both the exposure and mediator, as well as those in risk

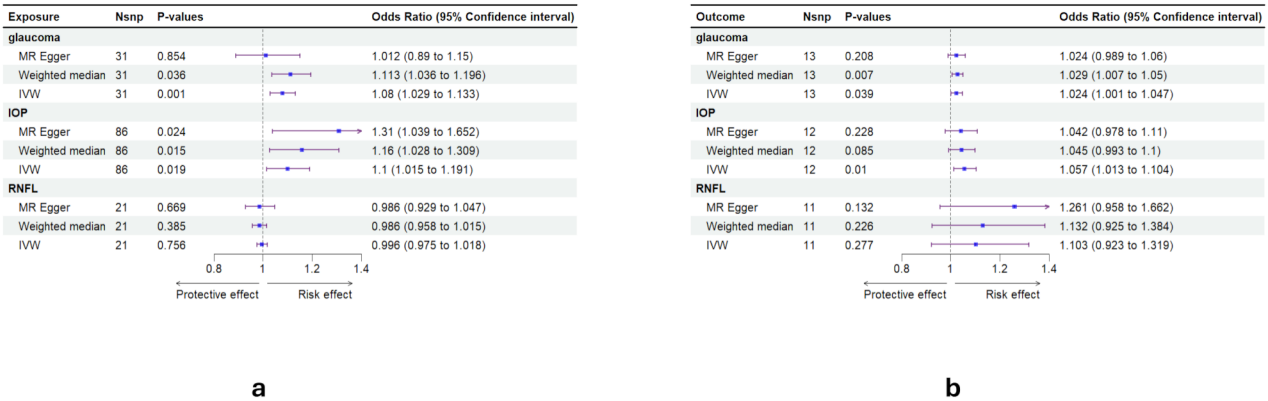

Fig. 2 Bidirectional MR results in forest plots. **(a)** The positive causal relationship between glaucoma and its characteristics and DR. **(b)** The reverse causal relationship between glaucoma and its characteristics and DR. IOP: intraocular pressure; RNFL: retinal nerve fiber layer; IVW:inverse-variance-weighted. Nsnp: the selected SNPs number of the exposure. P-values: the different methods in each subgroup, indicating statistical significance. Blue square indicates odds ratio and horizontal line indicates 95% confidence interval

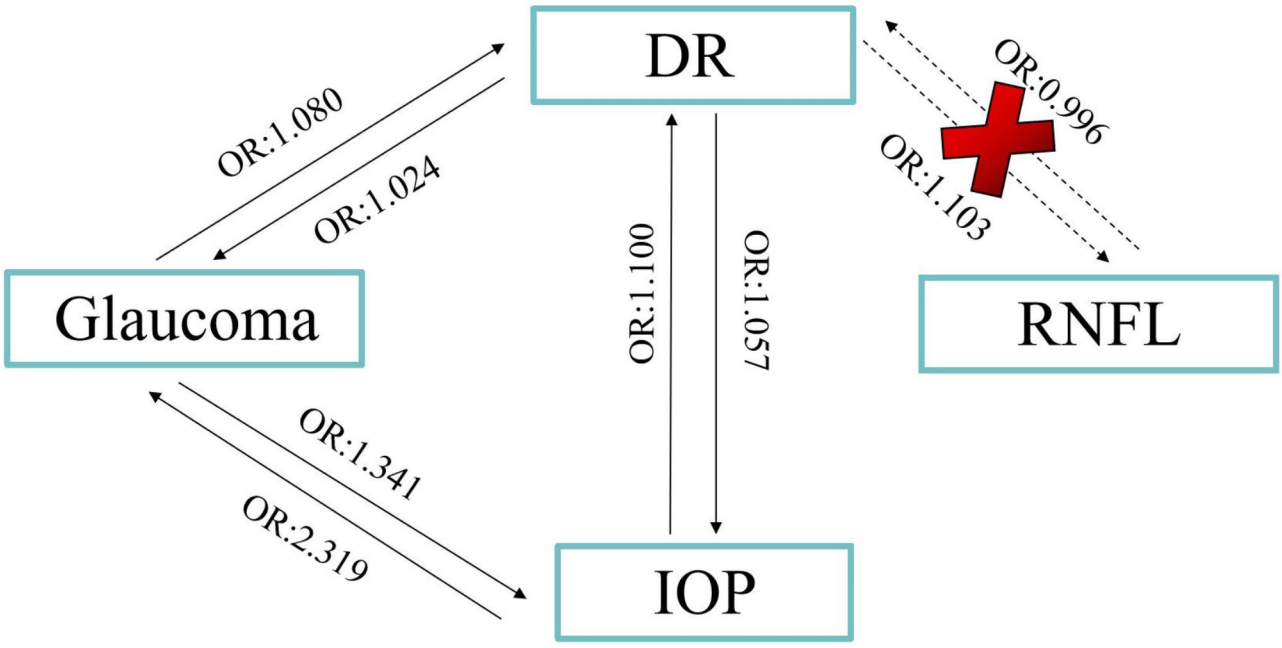

Fig. 3 The causal relationship between exposure and outcome. IOP: intraocular pressure; RNFL: retinal nerve fiber layer; DR: diabetic retinopathy; OR: odds ratio. The arrows point from the exposure to the outcome. OR represents the strength of the association between exposure and outcome. The red cross represents that there is no statistically significant causal relationship between exposure and outcome

Table 2 Multivariable Mendelian randomization results

	MVMR-IVW			MVMR-egger		
	OR	**95%CI**	***P*-values**	**OR**	**95%CI**	***P*-values**
IOP	1.036	0.993,1.160	0.536	1.091	0.960,1.239	0.177
Glaucoma	1.069	1.001,1.142	0.046	1.107	1.025,1.197	0.009

OR: odds ratio; CI: confidence interval; IOP: intraocular pressure; 95%CI: 95% confidence interval

Table 3 Mediation analysis result

Exposure	Mediator	Outcome	Mediation effect	Proportion mediated	*P*-values
Glaucoma	IOP	DR	0.027	36.11%	0.020
IOP	Glaucoma	DR	0.007	7.75%	0.061
DR	IOP	Glaucoma	0.020	35.77%	0.041
DR	Glaucoma	IOP	0.016	69.05%	0.011

Proportion mediated: the percentage of the mediating effect; IOP: intraocular pressure; DR: diabetic retinopathy

factors associated with the outcome. In the second step, we calculated the causal effect of exposure on the mediator. In the third step, we estimated the causal effect of the mediator on the outcome. Finally, the mediation effect and the percentage of the mediating effect were calculated and the reliability of the results was verified using hypothesis testing.

With glaucoma as exposure, IOP as mediator, and DR as outcome, the mediation effect was 0.027, proportion 36.11%, and p-value 0.020, indicating IOP's mediating role between glaucoma and DR. For DR as exposure, IOP as mediator, and glaucoma as outcome, the values were 0.020, 35.77%, and 0.041. When DR was exposed, glaucoma mediated, and IOP was outcome, they were 0.016, 69.05%, and 0.011. With the exception of the mediating effect of glaucoma-mediated IOP on DR, which did not reach statistical significance, all other mediating MR analyses yielded statistically significant results. These results support mediating roles, detailed in Table 3.

Discussion

As far as we know, this is the first study to investigate the causal relationships among glaucoma, IOP, RNFL, and DR using bidirectional MR analysis. We also examined the potential causal links between glaucoma, IOP, and DR via MVMR and two-step MR. Our findings indicate that glaucoma and IOP are genetic risk factors for DR, with glaucoma as an independent risk factor, and IOP mediating the relationship between glaucoma and DR risk. Similarly, IOP and DR are risk factors for glaucoma, reaffirming IOP's mediating role in the glaucoma-DR risk relationship. Furthermore, glaucoma significantly influences the causal relationship between DR and IOP.

In our MR study, glaucoma and IOP were significantly associated with an increased risk for DR. A prospective cohort study with a 5-year follow-up found that patients with glaucoma and/or high IOP, combined with type 2 diabetes mellitus (T2DM), are more likely to develop DR with 5 years compared to T2DM patients without glaucoma and/or high IOP [15]. High glucose concentration can damage the trabecular meshwork, leading to blockage of atrial aqueous outflow, and high serum/atrial aqueous osmolarity may lead to high IOP and glaucoma [16].

DR is often accompanied by elevated levels of inflammatory factors such as tumor necrosis factor, interleukin, and monocyte chemoattractant protein-1, along with glaucoma [17, 18]. The high concentration of these inflammatory factors in the eye exacerbates the damage to the eye caused by DR and glaucoma [19]. These inflammatory factors not only disrupt the tight junctions of endothelial cells and induce inflammatory cascades to destroy the blood-retinal barrier (BRB), but also stimulate the activation and migration of leukocytes, leading to capillary blockage, increased aqueous humor production or impaired aqueous humor outflow, and thereby inducing elevated IOP [20].

Elevated levels of vascular endothelial growth factor are a key pathological mechanism of DR, promoting vascular permeability and angiogenesis, leading to the disruption of the BRB. Dysfunction of the BRB results in fluid leakage and tissue edema, thereby affecting the regulation of IOP [21]. Moreover, high IOP can activate microglia through various pathways [22, 23], further enhancing the release of inflammatory factors [24, 25], which participate in the progression of DR and induce apoptosis of RGCs [26, 27]. DR, glaucoma, and IOP influence each other. Some scholars' clinical studies have confirmed the view that glaucoma and DR are mutual risk factors [7, 28]. The specific mechanism of action among them needs to be confirmed in future studies.

RGCs loss contributes not only to the pathogenesis of glaucoma but also to the development of DR. RGCs loss can be manifested by a decrease in RNFL thickness. A cross-sectional study found that RNFL thickness is reduced in diabetic patients compared to normal subjects. Additionally, T2DM patients without any signs of DR had thinner RNFL [29], suggesting that the occurrence of diabetic neuroretinopathy may precede vascular lesions [30]. The injury mechanisms of RGCs may be related to metabolic disorders of high sugar, oxidative stress, and deficiency of neurotrophic factors [31, 32].

Oxidative stress is a cellular pathological state caused by excessive production of reactive oxygen species (ROS) and antioxidant imbalance. Oxidative stress induced by hyperglycemia can activate multiple metabolic pathways, including the polyol pathway, hexosamine pathway, protein kinase C pathway, and accumulation of advanced glycation end products [33]. The activation of these pathways further increases the production of ROS, forming a vicious cycle [33]. Hyperglycemia induces mitochondrial dysfunction, leading to sustained production of ROS. DR is often accompanied by oxidative stress, which may damage RGCs through this pathway [34]. In this study, the OR estimate of RNFL for DR was less than 1, suggesting that RNFL may be a protective factor for DR, although this finding lacks statistical significance. This discrepancy may be attributed to the influence of various confounding factors. Therefore, further validation of this finding is necessary.

We provide robust insights into causal relationships among glaucoma, IOP, RNFL, and DR, informing clinical and public health decisions. Our findings can be used to develop new diagnostic tools and screening methods to help identify high-risk patients early, thereby enabling timely intervention and treatment. Moreover, by identifying genetic variants related to glaucoma and its traits with DR, we can better understand their pathogenic mechanisms, providing a basis for developing new therapeutic targets. Additionally, explaining genetic risks to patients can enhance their health awareness and compliance. Through education, patients can better manage their health and reduce the risk of disease progression.

MR is a valuable tool for causal inference in epidemiological research, offering a quasirandomized approach that mitigates many of the limitations of traditional observational studies. It addresses reverse causality by leveraging genetic determinants that are fixed at birth and unaffected by subsequent environmental influences [35]. Additionally, MR leverages the wealth of data from GWASs, allowing researchers to investigate a wide range of exposures and outcomes efficiently. It is also cost-effective and feasible compared to randomized controlled trials, as it relies on existing genetic data without the need for extensive resources or ethical concerns associated with interventions.

However, there are limitations to this paper. Firstly, the results of MR study only suggest a causal relationship between glaucoma, IOP, RNFL, and DR, but the underlying mechanisms remain unclear. Secondly, because the GWAS database does not provide raw data or sample information, we were unable to provide participant characteristics due to objective data limitations. Thirdly, our research is restricted to individuals of European ancestry. Consequently, when attempting to generalize the obtained results to a more heterogeneous and global population, one must exercise caution. This is due to the fact that genetic, environmental, and cultural differences among various ethnic groups could potentially influence the research outcomes, and thus, extrapolating our findings without due consideration may lead to inaccurate or misleading conclusions.

Conclusion

Based on the results of this study, we have determined that glaucoma and IOP are risk factors for DR. Specifically, IOP mediates the bidirectional causal relationship between glaucoma and DR. Additionally, DR serves as a risk factor for both glaucoma and IOP, and glaucoma mediates the positive causal relationship between IOP and DR. Our study offers a theoretical foundation for the interaction between glaucoma and DR.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01652-5 .

Supplementary Material 1

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Author contributions
C-SY: Conceptualization, Writing - original daft, Writing – review & editing. L-M: Conceptualization, Writing – review & editing. H-Y: Funding acquisition, Supervision, Writing – review & editing.

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Data availability
The original contribution presented in the study is included in the article/Supplement Material. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent to publication
Not applicable.

Conflict of interest
All authors declare that there are no competing interests.

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