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Association between myopia and diabetic retinopathy: A two-sample mendelian randomization study

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ABSTRACT

Objective: The association between myopia and diabetic retinopathy (DR) is unclear, with inconsistent results reported, and whether the association represents causality remains unknown. This study aimed to investigate the causal associations of genetically determined myopia with DR, and further explore specific mechanisms.

Methods: We conducted two-sample mendelian randomization (MR) analyses of any myopia and high myopia on six DR phenotypes, including any DR, background DR, severe background DR, proliferative DR (PDR), diabetic maculopathy and unspecific DR in the primary study. Mechanism exploration of spherical equivalent refraction (SER), corneal curvature (CC) and axial length (AL) on any DR was carried out subsequently. Single-nucleotide polymorphisms (SNPs), used as genetic instruments, were derived from UK Biobank, Genetic Epidemiology Research on Adult Health and Aging cohort (GERA) and FinnGen. The inverse variance weighted (IVW) method was mainly used to assess the causality, and was complemented with sensitivity analyses and causality direction analyses.

Results: Using SNPs that have excluded possible confounders, we discovered suggestive and positive causal associations of any myopia with any DR (IVW: odds ratio [OR] = 1.133, 95% confidence interval [95%CI]: 1.070–1.201, $P = 1.91\times10^{-5}$) and PDR (IVW: OR = 1.182, 95% CI: 1.088–1.285, $P = 8.31\times10^{-5}$). Similar but more significant associations were found of high myopia with any DR and PDR (IVW: OR = 1.107, 95%CI: 1.051–1.166, $P = 1.39\times10^{-4}$; OR = 1.163, 95%CI: 1.088–1.244, $P = 8.76\times10^{-6}$, respectively). Further mechanism analyses found only AL, rather than SER or CC, was strongly and significantly associated with any DR. These associations were robust in sensitivity analyses and causality direction analyses.

Conclusions: We found significant and positive causal associations of any myopia and high myopia with the risk of DR and PDR, which might be related with AL, indicating the significance of myopia control for preventing DR development and progression.

1. Introduction

Diabetic retinopathy (DR) is one of the primary causes of visual impairment and blindness worldwide, with the affected individuals projected to rise to 161 million by 2045.[1] This has brought a huge burden to the society and healthcare system. When effective treatment is not timely, DR may progress to irreversible central and peripheral vision loss,[2] emphasizing the importance of identifying its risk factors for early diagnosis and management.

Epidemiological studies have reported a variety of important factors that influence the development of DR, such as duration of diabetes, glycemic control, body mass index (BMI), hypertension, etc.[3] An association between myopia and DR has also been mentioned. Recent studies suggested that myopia and high myopia were protective factors against different stages of DR.[4,5] Moreover, most studies believed only the axial component of myopia played an important role in DR correlation.[6,7]

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However, the results were inconsistent and conflicting. The association of DR with refractive myopia has also been reported.[8] Additionally, the cohort study from Man et al. indicated no association of myopia on DR.[9] This discrepancy among previous studies might be due to biases or confounders that couldn't be completely rule out in observational epidemiological studies, such as small sample size, heterogeneity in demographic characteristics, selection bias and reverse causality.[10]

Mendelian randomization (MR) analysis has become a popular and practical method for causal inference. It utilizes genetic variations as instrumental variables (IVs) and takes advantage of the inherent random segregation of alleles, allowing genetic associations to be independent of confounding factors and reverse causation.[11] Moreover, MR studies can largely imitate randomized clinical trials, and the findings are generally consistent.[12] Since both myopia and DR are heritable,[13,14] MR is an ideal approach which can overcome some of the limitations of observational studies and establish causal link. However, there have been no MR studies evaluating the observational correlations between myopia and DR.

In this study, we first conducted a primary study on myopia and DR to see whether a causal relationship exists. A two-sample MR approach of any myopia and high myopia on the risk of six DR phenotypes, including any DR, background diabetic retinopathy (BGDR), severe background diabetic retinopathy (SBGDR), proliferative diabetic retinopathy (PDR), diabetic maculopathy (DMP) and unspecific diabetic retinopathy (UDR) was employed. To further understand whether axial, or refractive myopia, or both, was the main contributor to this causal link, we subsequently carried out mechanism exploration of spherical equivalent refraction (SER), corneal curvature (CC) and axial length (AL) on any DR using MR analysis. This might give us a better understanding of the relationship between myopia and DR, deepen our awareness of DR pathophysiology, and have public health and clinical implications for prevention and early detection of this common cause of visual disability.

2. Methods

2.1. Study design

This study is a univariable two-sample MR analysis. Using summary statistics from genome-wide association studies (GWASs), we investigated the causal associations of any myopia and high myopia with six DR phenotypes (any DR, BGDR, SBGDR, PDR, DMP and UDR) in the primary study, and the causality of SER, CC and AL with any DR in the mechanism exploration. A schematic diagram outlining the process is presented in Fig. 1. Furthermore, we have adhered to the MR-STROBE guidelines in reporting our findings.[15]

2.2. GWAS data source

Brief information of the exposures and outcomes are displayed in Table 1.

Summary statistics of any myopia, high myopia, SER and CC were all obtained from lately published GWASs using data from the UK Biobank (UKB, https://www.nealelab.is/uk-biobank). The UKB is a large, prospective and population-based cohort of 502,413 participants aged 40–69 years recruited from 2006 to 2010. Details of the study design and protocols could be found elsewhere.[16] In UKB, non-cycloplegic autorefraction and keratometry was measured directly using the Tomey RC 5000 Auto-Refractor Keratometer (Tomey Corporation, Aichi, Japan).

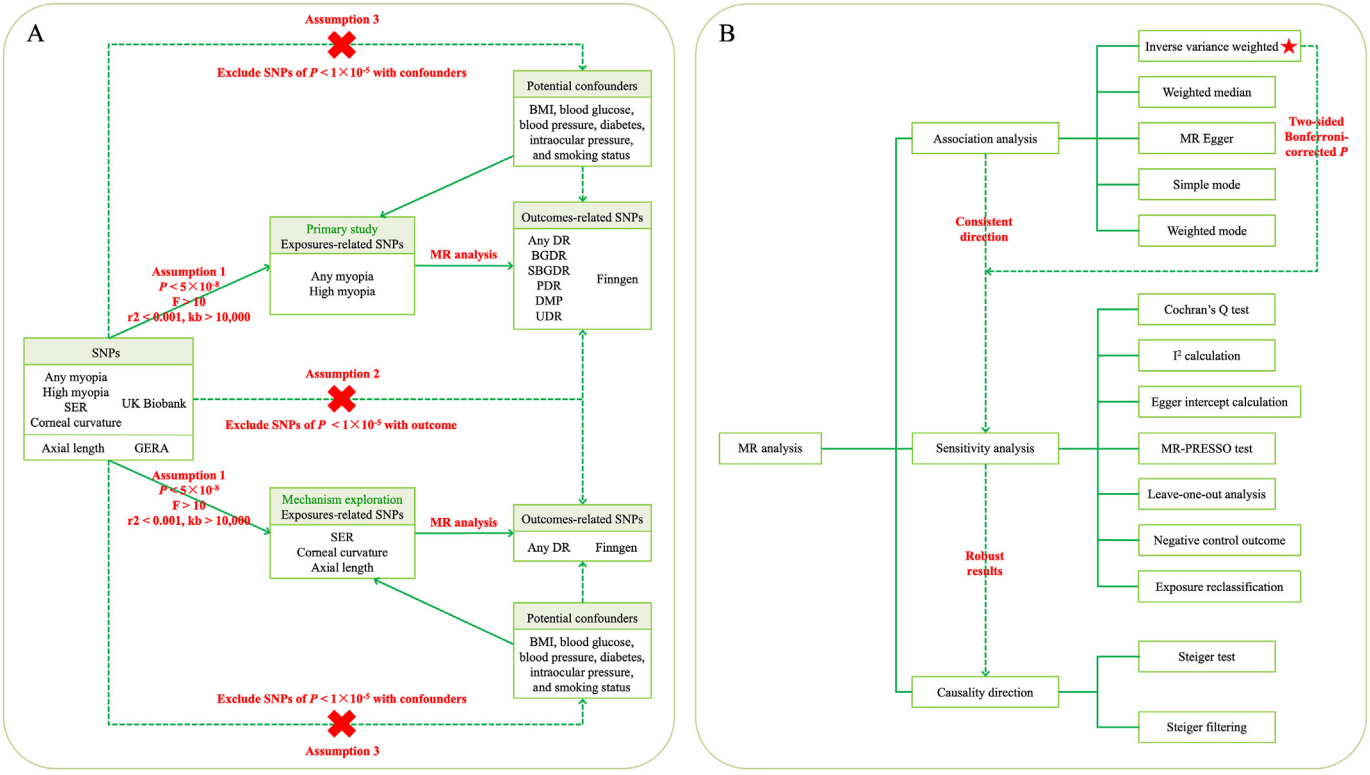

Fig. 1. Workflow of MR study revealing the causality of myopia on DR. (A) The exposures, outcomes, potential confounders, principles, and assumptions of MR; (B) The process of MR analysis. Significance for strong evidence was defined as two-sided Bonferroni-corrected $P < 4.17\times10^{-3}$ for primary study and two-sided Bonferroni-corrected $P < 1.67\times10^{-2}$ for mechanism exploration. Significance for suggestive evidence was defined as $4.17\times10^{-3} \leq P < 0.05$ for primary study and $1.67\times10^{-2} \leq P < 0.05$ for mechanism exploration (two-sided Bonferroni-corrected *P*). Error symbol indicates no correlation. Asterisk indicates the most important. Abbreviations: SNP, single nucleotide polymorphism, GERA, Genetic Epidemiology Research on Adult Health and Aging; SER, spherical equivalent refraction; BMI, body mass index, DR, diabetic retinopathy; BGDR, background diabetic retinopathy; SBGDR, severe background diabetic retinopathy; PDR, proliferative diabetic retinopathy, DMP diabetic maculopathy, UDR, unspecific diabetic retinopathy; MR, mendelian randomization; MR-PRESSO, mendelian randomization pleiotropy RESidual sum and outlier.

Table 1
Description of GWAS summary statistics for exposures and outcomes.

Trait	Variable type	Sample size (case/control)	Population Ethnicity	Consortium	Study[b]/GWAS ID[c]
Any myopia	Exposure	27993/36275	European	UK Biobank	PMID: 35841873
High myopia	Exposure	3164/21416	European	UK Biobank	PMID: 33830181
SER	Exposure	102117[a]	European	UK Biobank	PMID: 32231278
Corneal curvature	Exposure	88218[a]	European	UK Biobank	PMID: 32193507
Axial length	Exposure	16523[a]	European	GERA	PMID: 37351342
Any DR	Outcome	12242/289034	European	Finngen	finngen_R7_DM_RETINOPATHY
BGDR	Outcome	3098/296912	European	Finngen	finngen_R7_DM_BCKGRND_RETINA
SBGDR	Outcome	672/296912	European	Finngen	finngen_R7_DM_BCKGRND_RETINA_NONPROLIF
PDR	Outcome	7349/296912	European	Finngen	finngen_R7_DM_RETINA_PROLIF
DMP	Outcome	2790/296454	European	Finngen	finngen_R7_DM_MACULOPATHY
UDR	Outcome	2719/296912	European	Finngen	finngen_R7_DM_RETINA_NOS

Abbreviations: GWAS, genome-wide association studies; SER, spherical equivalent refraction; GERA, Genetic Epidemiology Research on Adult Health and Aging; DR: diabetic retinopathy; BGDR: background diabetic retinopathy; SBGDR: severe background diabetic retinopathy; PDR: proliferative diabetic retinopathy; DMP: diabetic maculopathy; UDR: unspecific diabetic retinopathy.

[a] SER, corneal curvature and axial length are continuous variables, contain only the total sample size.

[b] GWAS summary datasets of exposures are from Pubmed (https://pubmed.ncbi.nlm.nih.gov/), do not have GWAS ID.

[c] GWAS summary datasets of outcomes are from the Finngen database (https://r7.finngen.fi/), possess GWAS ID.

The spherical equivalent was estimated as the sphere power (UKB codes 5084 and 5085) plus half the cylinder power (UKB codes 5086 and 5087) for each eye, with mean spherical equivalent (MSE) averaged between fellow eyes. The keratometry was reported as the maximum (UKB codes 5132 and 5135) and minimum (UKB codes 5096 and 5099) corneal power in each eye.[17] For any myopia, participants with MSE ≤ -0.50D were identified as cases, while participants with MSE > -0.50D and didn't have any ocular disease were controls.[18] GWAS for high myopia (MSE: −6.00D or less) comprised 3164 cases and 21416 emmetropia controls (MSE: 0.00 to +1.00D).[19] As for SER (continuous variable, per 1D decrease as unit), MSE was used as the outcome of the GWAS analysis.[14] Another continuous variable, CC (per 1 mm decrease as unit), was converted by equation (337.5)/corneal power, and the average CC of the two eyes was taken as the phenotype.[20]

We obtained the AL data of 16523 European participants from a large multiethnic GWAS consisting of 19420 individuals from the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort.[21] The GERA cohort, containing 110266 adults, is established by Kaiser Permanente Medical Care Plan, Northern California Region (KPNC), an integrated health care delivery system with >3 million members (https://researchbank.kaiserpermanente.org/).[22] Haag-Streit Lenstar 900 was applied to measure AL, and the mean AL (per 1 mm increase as unit) of an individuals' two eyes was used for the analysis.

The GWAS summary statistics for DR were sourced from the FinnGen (https://r7.finngen.fi/), a large-scale research project including genome and health data from 500000 Finnish biobank participants.[23] DR was identified using the International Classification of Diseases-Revision 10 (ICD-10) criteria from the hospital discharge registry. Participants in any DR (ICD-10: H36.0) analysis included 12242 cases and 289034 controls. Based on different levels of DR severity, four DR phenotypes were selected: BGDR (ICD-10: H36.00), DMP (ICD-10: H36.01), SBGDR (ICD-10: H36.02) and PDR (ICD-10: H36.03). Additionally, we also used UDR (ICD-10: H36.09) as our outcome. As for the controls, people without DR including healthy and individuals with diabetes were enrolled. Further details have been described elsewhere (https://finngen.gitbook.io/documentation/v/r7/).

The data and information we used in this article were all searched and downloaded from the public database. No ethical review was required for this study.

2.3. Selection of SNPs

Single-nucleotide polymorphisms (SNPs) were selected to represent instrumental variables (IVs) in our study. To attain unbiased causal effects, MR must be in accordance with three core assumptions (Fig. 1): (1) SNPs are strongly associated with the exposure; (2) SNPs must influence the outcome only through the exposure of interest; (3) SNPs are not related to potential confounders.[24]

SNPs must meet the following criteria to fulfil the three basic MR assumptions: (1) SNPs for exposure must satisfy $P < 5\times10^{-8}$[25]; (2) $F > 10$ to establish a strong association between SNPs and exposure, and avoid weak instrument bias[26]; (3) Linkage disequilibrium $r^2 < 0.001$ and linkage disequilibrium distance >10000 kb to ensure independence between SNPs[27]; (4) SNPs of $P < 1\times10^{-5}$ with the outcome must be removed to exclude association with outcome[28]; (5) Exclude SNPs associated with potential confounders ($P < 1\times10^{-5}$)[29,30] using the GWAS Catalog database (https://www.ebi.ac.uk/gwas/)[31] and the IEU Open GWAS Project database (https://gwas.mrcieu.ac.uk/).[32] Only GWASs restricted to European ethnicity were considered.[33,34] We have included BMI,[35,36] blood glucose,[37,38] blood pressure,[39] diabetes,[40] intraocular pressure[41] and smoking status[42] as potential confounders, since these factors have been identified to be related with myopia, or DR, or both.

2.4. MR analysis

All analyses were performed using the TwoSampleMR package (version 0.5.8) and MendelianRandomization package (version 0.9.0) in R (R Foundation for Statistical Computing, Vienna, Austria, version 4.3.2). The packages harmonize exposure and outcome datasets, and make causal inference, sensitivity analysis and directional analysis using GWAS summary statistics.

We used inverse variance weighted (IVW), the most efficient (greatest statistical power) method,[43] as our primary result. This method rules out the presence of intercept and uses inverse variance of the outcome effect for weighted regression. Then, we presented the weighted median,[44] a method that provides valid estimates when at least 50% of information is derived from valid SNPs. Moreover, we have also applied three additional methods including MR Egger,[45] simple mode and weighted mode.[46] However, these methods have less statistical power than IVW, leading to very wide confidence interval (CI), and hence we focused more on the consistency of the estimate direction.[47] Ultimately, the causal estimates were expressed as odds ratio (OR) along with corresponding 95%CI. On the premise that all five MR methods had effects in the same direction (all $OR > 1$ / < 1), MR results were considered significant for strong evidence if the IVW and weighted median methods satisfied a two-sided Bonferroni-corrected $P < 4.17\times10^{-3}$ [0.05/(2×6)] for primary study or $P < 1.67\times10^{-2}$ [0.05/(3×1)] for mechanism exploration, and considered suggestive when $4.17\times10^{-3} \leq P < 0.05$ for primary study or $1.67\times10^{-2} \leq P < 0.05$ for mechanism exploration.[48]

Sensitivity analysis is crucial for ensuring the robustness of association results in MR research.[43] We employed Cochran's Q test and I^2 calculation to evaluate potential heterogeneity among SNPs. Cochran

Q-derived $P > 0.05$ in IVW method and $I^2 < 25\%$ indicates no heterogeneity. The relative symmetry around the vertical line corresponding to IVW method of funnel plots was also used to visualize the absence of heterogeneity. Horizontal pleiotropy was detected utilizing Egger intercept calculation by examining whether the intercept significantly deviated from zero. If the intercept shows no significant difference from zero ($P > 0.05$), there's no pleiotropy. Moreover, Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test was applied to evaluate horizontal pleiotropy (Global Test $P > 0.05$ indicates no pleiotropy), detect outliers and re-assess causality after excluding the outliers. To determine whether a single SNP dominated the causal association, we also conducted a leave-one-out analysis in which IVW analysis was repeated with the omission of each exposure-related SNP in turn. Two additional approaches for assessing robustness included the use of income, education and intelligence level as negative control outcomes, and the swap of exposed and unexposed populations.

Finally, we applied MR-Steiger methods (Steiger test and Steiger filtering)[49] to explore whether a reverse causal relationship existed, and whether the association of SNP with outcome was stronger than that with the exposure.

3. Results

3.1. SNPs for myopia and DR

Our strict SNPs screening process was based on the five standards mentioned above to meet the three major assumptions. Beyond that, some SNPs were removed due to no corresponding data in outcome GWAS datasets, incompatible alleles with outcome GWAS datasets and containing palindromic sequences.[50] After clumping, 7 SNPs for high myopia and 26 SNPs for any myopia were chosen for final MR analysis on DR (any DR, BGDR, SBGDR, PDR, DMP and UDR) in the primary study. As for the mechanism exploration, 11 SNPs for AL, 20 SNPs for CC and 84 SNPs for SER were used for causal inference with any DR. Detailed information of the SNPs is provided in Tables S1–S5.

3.2. Causal effects of myopia on DR in the primary study

The associations of myopia with DR are demonstrated in Supplementary Fig. 1. Only suggestive evidence indicated that the genetically predicted incidence of any myopia was significantly and positively associated with any DR and PDR, since IVW alone satisfied $P < 4.17\times10^{-3}$ (OR = 1.133, 95%CI: 1.070–1.201, $P = 1.91\times10^{-5}$; OR = 1.182, 95%CI: 1.088–1.285, $P = 8.31\times10^{-5}$, respectively) while weighted median satisfied $4.17\times10^{-3} \leq P < 0.05$ (OR = 1.100, 95%CI: 1.010–1.198, $P = 0.028$; OR = 1.121; 95%CI: 1.003–1.253; $P = 0.043$, respectively). The uniform direction of ORs (all >1) using MR Egger, simple mode and weighted median further confirmed its adverse role against any DR and PDR.

We have found strong evidence for causal effects of high myopia on both any DR risk and PDR risk, as the existence of high myopia was more likely to result in higher risk of any DR (IVW: OR = 1.107, 95%CI: 1.051–1.166, $P = 1.39\times10^{-4}$; weighted median: OR = 1.122, 95%CI: 1.049–1.201, $P = 7.88\times10^{-4}$) and PDR (IVW: OR = 1.163; 95%CI: 1.088–1.244; $P = 8.76\times10^{-6}$; weighted median: OR = 1.164, 95%CI: 1.067–1.270, $P = 6.56\times10^{-4}$), respectively. The other three MR methods all revealed OR > 1, which further supported this conclusion. No other associations were found between myopia and DR.

Scatter plots and forest plots were applied in our study to provide a more intuitive representation of the correlation between myopia and DR, as well as the effect size and 95%CI for each SNP (Fig. 2; Fig. S2).

3.3. Sensitivity analysis and causality direction in the primary study

We have conducted further analyses on the exposures and outcomes that showed significant correlations in MR association analysis to assess the robustness of the causal relationships. The Cochran's Q test and I^2 calculation of any myopia and any DR, high myopia and any DR, and high myopia and PDR all showed no heterogeneity (all $P > 0.05$, $I^2 < 25\%$). Although the I^2 calculation between any myopia and PDR was greater than 25% ($I^2 = 27.2\%$), indicating a possible degree of heterogeneity, the Cochran Q-derived $P > 0.05$ in IVW method suggested nearly acceptable robustness (Table 2). Additionally, funnel plots displayed symmetrical distribution in Fig. S3, visually represent the absence of heterogeneity. Our assessment through Egger intercept calculation yielded no evidence of horizontal pleiotropy (all $P > 0.05$), which could be confirmed by MR-PRESSO, as depicted in Table 2. Moreover, no outliers were identified through MR-PRESSO. According to the leave-one-out analysis, no single SNP significantly deviated from the overall impact of myopia on DR (Fig. 3). The two additional sensitive analyses testified the robustness of the results as well (Tables S6–S7). Also, MR-Steiger results showed that the selected SNPs were valid instruments for the exposures and that the causal estimates were oriented in the expected direction (Table 2; Tables S8–S9). Taken together, these results corroborate the causal link between any myopia and any DR, any myopia and PDR, high myopia and any DR, and high myopia and PDR.

3.4. MR analysis in the mechanism exploration

Only AL, rather than SER or CC, was found to be strongly and significantly associated with any DR (Fig. S1; Fig. S4). The main IVW method suggested a positive causality (OR = 1.168; 95%CI: 1.047–1.302; $P = 5.23\times10^{-3}$), supported by weighed median (OR = 1.177; 95%CI: 1.031–1.343; $P = 1.61\times10^{-2}$) and all the other three methods showing effects in the same direction (OR > 1). We then tested the heterogeneity and found $P = 0.15$ (> 0.05) for Cochran's Q test and symmetrical distribution around IVW in funnel plot, indicating barely any heterogeneity although $I^2 = 31.2\%$ (> 25%). Additionally, all the other sensitive analyses and causality direction verification evidenced the robustness of causal association between AL and any DR (Table 2; Tables S6–7; Table S10; Fig. S4).

4. Discussion

This study is, to our knowledge, the first to investigate the causal associations of myopia with the risk of DR leveraging the MR method. Our main findings, consistent with the sensitivity analyses, demonstrated that a genetic predisposition to any myopia was suggestively associated with increased risk of any DR and PDR. We also found strong genetic evidence for potential promoting causal effects of high myopia on any DR and PDR. Further, the MR-Steiger results strongly supported the directionality of causality and proved no reverse causal relationship. The underlying mechanism behind this causal link might be related to AL instead of SER or CC.

Two-sample MR analysis, in which variant-exposure associations are estimated in one dataset and variant-outcome associations are estimated in a different dataset, was used in our study. With the increasing abundance of publicly available summarized data from large consortium, this approach has become an attractive analytical strategy.[51] Compared with one-sample MR, which needs individual-level data of genetic variants, exposure and outcome measured in the same participant, two-sample MR possesses easier data acquisition. More advantages include avoiding underestimate true causal effects, pulling weak instrument biases towards the null, and increasing statistical power.[52] However, if sample overlap exists when using two-sample MR, some of the advantages will be potentially lost.[53] We believed there was limited sample overlap between myopia and DR data, since the exposure GWASs were from the FinnGen study and the GERA cohort which included individuals from Finnish and the United States respectively, while the outcome data were derived from UK Biobank GWAS of several centers in Britain.

Myopia has emerged as a public challenge worldwide, with individuals suffering from visual impairment.[54] Further vision challenges

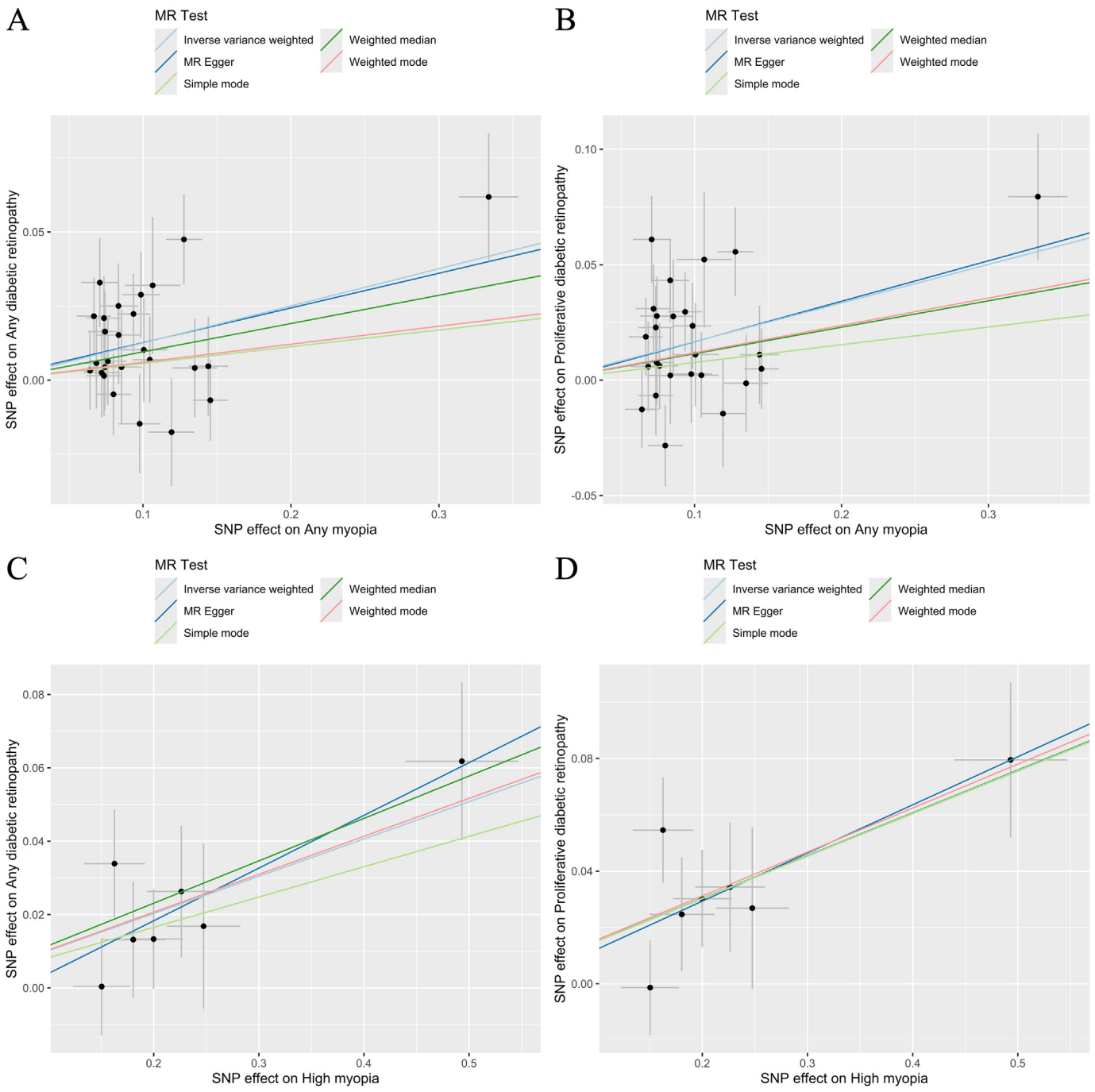

Fig. 2. Scatter plots for MR analyses of the causal effects of myopia on DR in the primary study. (A) Any myopia on any DR; (B) Any myopia on PDR; (C) High myopia on any DR: (D) High myopia on PDR. Abbreviations: MR, mendelian randomization; SNP, single nucleotide polymorphism; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy.

have been brought by high myopia given its promotion of myopic complications and ocular diseases such as retinal detachment, macular degeneration, cataract and open angle glaucoma, all of which can cause irreversible vision loss.[55] In the primary study, we innovatively highlighted the suggestive significance of any myopia on higher risk of any DR and its advanced form PDR, and identified high myopia as potential risk factor for any DR and PDR with strong evidence. The variation in evidence efficacy might be attributed to high myopia being more prone to pathological changes, damaging eye structures such as retina, and thus is more significantly associated with DR.[56] Previous observational studies[4,5] and meta-analyses[57] have demonstrated protective effect of myopia and high myopia against DR. However, these studies recruited people with diabetes as controls, while in our study, the controls are people without DR including healthy population and individuals with diabetes. Also, our participants are Europeans, while most previous studies were conducted in Asian people. This may partly explain the difference of effect direction. Furthermore, there are also some studies indicating no association of myopia with DR,[9,58] which might be due to the small sample size, cross-sectional nature and inherent bias of these observational studies, whereas our MR study has overcome these limitations and discovered the causal associations.

Whether refractive, or axial myopia, or both leads to the association with DR is still up for debate. No association has been determined between SER and any DR, which is similar to current studies.[9,57] Because

Table 2
Sensitivity analysis and causality direction of significantly correlated exposures and outcomes.

Exposures	Outcomes	Methods						
		P_Heterogeneity	I^2 calculation	P_Pleiotropy	MR-PRESSO test		Steiger test	
					P_Global test	Outlier	Causal direction	P_Steiger
Any myopia	Any DR	0.409	3.7%	0.908	0.395	No outlier	TRUE	1.27E-255
	PDR	0.116	25.7%	0.934	0.135	No outlier	TRUE	4.28E-252
High myopia	Any DR	0.741	0.0%	0.536	0.784	No outlier	TRUE	3.83E-60
	PDR	0.570	0.0%	0.819	0.673	No outlier	TRUE	7.48E-59
Axial length	Any DR	0.150	31.2%	0.282	0.171	No outlier	TRUE	2.46E-93

Abbreviations: DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; P_Heterogeneity, *P*-value for heterogeneity using Cochran's Q test in IVW method; P_Pleiotropy, *P*-value for pleiotropy using Egger intercept calculation; MR-PRESSO, mendelian randomization pleiotropy RESidual sum and outlier; P_Global test, *P*-value for pleiotropy using MR-PRESSO test; P_Steiger, *P*-value for determining whether the causal direction is correct using Steiger test.

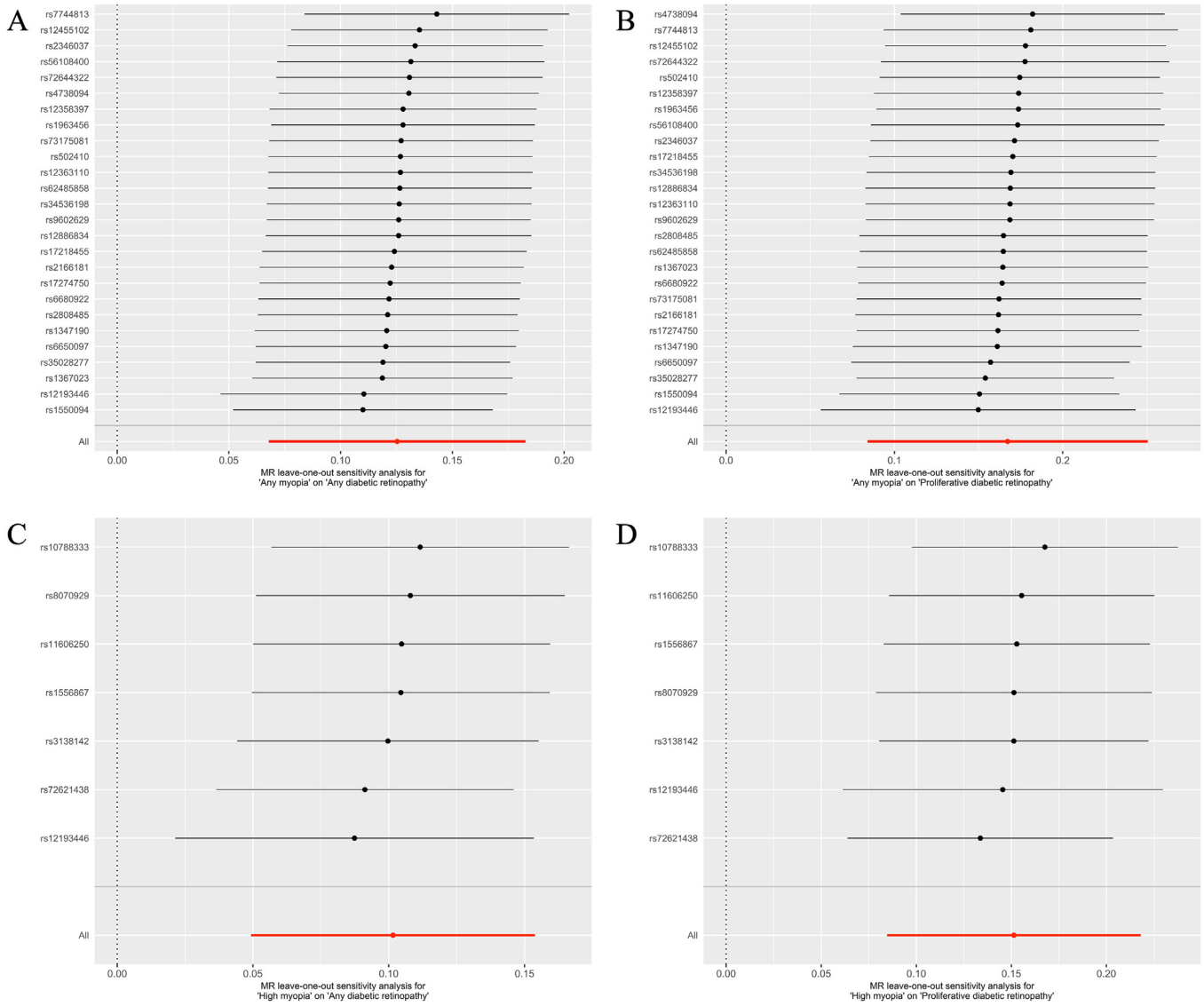

Fig. 3. Leave-one-out analysis of the causal effects of myopia on DR in the primary study. Each black point represents the IVW estimate excluding a particular SNP from the analysis. The red point represents the IVW estimate using all SNPs. (A) Any myopia on any DR; (B) Any myopia on PDR; (C) High myopia on any DR; (D) High myopia on PDR. Abbreviations: MR, mendelian randomization; SNP, single nucleotide polymorphism; IVW, inverse variance weighted; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy.

SER contains both refractive and axial components, this result indicated no synergistic effect of the two components on DR. Further analysis on CC found no causal link with DR, opposing the role of refractive myopia, as reported previously.[59] AL has been found to possess a dose-dependent negative correlation with DR.[7] Additionally, both review and recent meta-analysis suggested that AL, but not SER, was negatively associated with DR.[6,57] Similarly, our MR study confirmed that the potential mechanism of causal association between myopia and DR lied in AL.

Further researches are needed to validate our results.

Several underlying pathophysiological mechanisms might explain the association between myopia and DR. Studies have reported that in pathological myopia, due to the axial elongation, the retinal arterioles became straightened and protruded anteriorly, and capillary telangiectasia and retinal capillary microaneurysms were frequently seen.[60] Blood vessels were vulnerable to rupture under these abnormal changes, and meanwhile, they were subject to aberrant compression that might damage the retinal capillary wall.[61] These factors might make myopias more prone to retinal microvascular leakage and fundus hemorrhage, characteristic manifestations of DR.[62] Another hypothesis is that oxidative stress in hypoxia environment caused by myopia might be necessary for DR. Increased AL and reduced scleral thickness during myopia would gradually cause atrophy of the choroid and retinal pigment epithelium, leading to hypoxia.[63] The subsequent production of reactive oxygen species (ROS) and lipid peroxidation products, and reduction of superoxide dismutase (SOD), nitric oxide synthase (NOS), and NO proposed an essential role of oxidative damage.[64] This oxidative stress condition has also been highlighted important in triggering the occurrence of DR.[65] Furthermore, proinflammatory cytokines and angiogenic growth factors such as vascular endothelial growth factor (VEGF), interferon-gamma (IFN-γ), and interleukin-6 (IL-6), which make significant contribution towards retinal neovascularization of DR, have been found with elevated level in the vitreous humor of high myopia people.[66]

Given the high and increasing prevalence of myopia and DR worldwide, and both being one of the main factors in vision impairment, exploring their relationship and the underlying mechanism may have considerable public health implications. Understanding which factors increase the risk of DR could not only help identify high-risk individuals but also help develop preventative strategies. In our study, any myopia and high myopia have been indicated to increase the risk of any DR and PDR, respectively. Also, it was AL that result in the causal association. This could emphasize the importance of myopia control, particularly AL control. Moreover, it may improve the awareness of individuals with myopia, especially high myopia, on the importance of regular fundus screening.

Some limitations should be acknowledged. First, this study was only conducted among Europeans, so further investigation is needed to see whether our findings are generalized in other racial groups. Second, our findings of the MR analysis are based solely on genetic evidence and has not been validated by other studies yet. Finally, even MR method cannot completely exclude the possibility of residual confounding factors.

5. Conclusions

In conclusion, our study provides supportive evidence for any myopia and strong evidence for high myopia of their potential causal associations with the increased risk of DR and PDR, which might be related with AL. The prevention of myopia, especially the development of high myopia and the elongation of AL, may be crucial to reduce the risk of onset and progress of DR. Future prospective and laboratory studies are needed to validate our findings.

Study approval

Not Applicable.

Author contributions

The authors confirm contribution to the paper as follows: JYX, SSX, XW: study concept and design, acquisition of data, statistical analysis, interpretation of data, drafting of the manuscript. CQX, ZBR, MXL, LYH: acquisition of data, interpretation of data. YH, XY: acquisition of data, interpretation of data, critical revision of the manuscript, administrative support and study supervision. All authors reviewed the results and approved the final version of the manuscript.

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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.

Data availability statement

The data of exposures that support the findings of this study are available in PubMed at https://pubmed.ncbi.nlm.nih.gov/. These data were derived from the following resources available in the public domain: https://doi.org/10.1016/j.ebiom.2022.104161, reference number PMID: 35841873; https://doi.org/10.1001/jamaophthalmol.2021.0497, reference number PMID: 33830181; https://doi.org/10.1038/s41588-020-0599-0, reference number PMID: 32231278; https://doi.org/10.1038/s42003-020-0802-y, reference number PMID: 32193507; https://doi.org/10.3389/fgene.2023.1113058, reference number PMID: 37351342. The data of outcomes that support the findings of this study are available in the FinnGen at https://r7.finngen.fi/.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aopr.2024.10.003.

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